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A STUDY OF JAUNDICE IN SYPHILIS.

ITS RELATION TO THERAPY.

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THE occurrence of jaundice in early syphilis has been reported as a rare complication of the disease since the 16th century, and its appearance with late syphilis of the liver, especially syphilitic cirrhosis, is not uncommon. Shortly after the advent of arsphenamin, jaundice following its administration was reported,[1, 2, 3] but it was not until the World War that icterus began to be a frequent complication. Scott and Pearson[4] reported 39 cases of jaundice out of 2243 patients treated, an incidence of 1.7 per cent, while Pulvermacher[5] reported an incidence of 2.75 per cent over a period of 15 months.

Prior to this time most cases had been thought to be entirely due to the toxic effect of the drug. The advent of epidemics of infectious or so-called "catarrhal" jaundice in the armies, and later in civilian populations, added a problem to the diagnosis, and led some to think that many cases were on the basis of an intercurrent infectious hepatitis. The question of hepatorecurrence, the rôle of heavy metal, the effect of infections in general, and previous liver damage are problems that we have studied in the following groups of patients with jaundice: (*a*) Untreated cases of jaundice

and syphilis; (*b*) jaundice following treatment for syphilis with one of the arsphenamins; (*c*) infectious jaundice; (*d*) syphilities who develop jaundice during or after malarial therapy.

The material for the study has been compiled from the records of the University Hospital, covering the period from January 1, 1925, to March 1, 1933. The cases are consecutive, with no attempt at selection.

Syphilis With Jaundice. An examination of the hospital records shows that we have seen 10,021 cases of syphilis in the period studied (4.3 per cent of all admissions). These cases were diagnosed as follows:

TABLE 1.—TYPE OF SYPHILIS ENCOUNTERED.

	No. of cases.
Latent	5,460
Central nervous system	1,680
Active (primary and secondary)	1,065
Congenital	1,040
Cardiac	385
All other types	391
Total	10,021

In this entire group the diagnosis of syphilis of the liver was made either clinically, following operation, or at autopsy in 91 cases, a percentage incidence of 0.9. This includes all types of hepatic syphilis and is, in our opinion, a low figure, not representing the true incidence of liver syphilis. In fact, it is difficult to see how any organ as vascular as the liver can escape involvement early, or not show evidence of syphilis later upon postmortem examination. Many are definitely occult, as proven by postmortem examination.[6] Inadequate knowledge of liver physiology, the absence of a satisfactory test for hepatic function, the large margin of hepatic reserve, and the known regenerative ability of the liver combine in making a diagnosis of syphilis of the liver difficult. Tests of hepatic function have been discussed in detail by O'Leary, Green and Rowntree.[7] In brief, we must rely upon disturbance of biliary or glycogenic function, change in size of the liver or a disturbance of portal circulation for the clinical diagnosis. These give us evidence of liver damage only when the process is extensive.

The types of cases of hepatic syphilis are shown in Table 2.

TABLE 2.—TYPES OF SYPHILIS OF THE LIVER ENCOUNTERED.

	No. of cases.
Early hepatitis:	
Icterus gravis	0
Benign	5
Chronic hepatitis:	
Diffuse interstitial	65
Gummous	10
Cirrhosis—all types	9
Banti's syndrome with syphilis	2
Total	91

Of the 5 cases of hepatitis in active secondary syphilis, only 2 were jaundiced, and 1 of these had a septic infection following a a recent abortion. In both cases the jaundice responded fairly promptly to heavy metal therapy. The other 3 cases, with enlarged firm livers, were given initial heavy metal therapy and did not develop jaundice subsequently. In 2 cases it was noted that the liver returned to normal size.

Of 65 cases of diffuse interstitial hepatitis, in 7 the diagnosis was made only at autopsy. Serologic tests were taken on but 4 of these and were positive in only 1 who had congenital syphilis. Of the remaining 58, the diagnosis rests upon a firm and palpable liver associated with other signs of syphilis. Only 1 of these cases later came to autopsy with confirmation of the diagnosis microscopically. In this group, only 3 cases had a clinical icterus. In 1 case the diagnosis was not confirmed by further studies. In a second the surgical department favored a diagnosis of obstructive jaundice; the exact cause was not determined. The third case responded to specific therapy. Two others had elevated blood bilirubins, 8 and 10 mg. per 1000 cc. respectively, but no clinical icterus. They were treated with mercury and iodids at the time and did not subsequently develop jaundice.

In the group of cases with gummous hepatitis, 1 had deep jaundice, fading rapidly after administration of mercury and potassium iodid; a second gave a definite history of transient jaundice shortly before, but could not be further studied. Only 1 case came to autopsy and the diagnosis of gummous hepatitis was confirmed.

In the group diagnosed as syphilitic cirrhosis, 6 cases had physical signs of portal obstruction and 2 of these also were slightly jaundiced; 2 others presented jaundice without portal obstruction; in 1, a patient with congenital syphilis—not jaundiced—a postmortem diagnosis of Hanot's cirrhosis was made; in 4, the diagnosis was confirmed by autopsy. Two patients have been treated specifically, with apparent good results.

There were 2 cases with Banti's syndrome with syphilis, both showing some response to antiluetic therapy. One relapsed when specific treatment was withdrawn and again improved when it was resumed.

In all, then, of the 91 cases of hepatic syphilis, only 13 had clinical jaundice, 2 had slightly elevated blood bilirubins only, and 1 gave a definite history of recent jaundice. None of these 16 had ever received antiluetic therapy before admission to the clinic. Our incidence of jaundice with hepatic syphilis is thus 17 per cent. In 2 cases the question of "catarrhal jaundice" was raised, and it might be added that 2 additional cases of syphilis with supposedly catarrhal or infectious jaundice were excluded in our subsequent group of infectious hepatitis. Since our purpose is to establish the frequency of pre-therapeutic jaundice, we will count them here.

Our incidence of jaundice then before treatment is 0.18 per cent (18 in 10,021 cases). This is lower than Werner's[8] report of an incidence of 0.37 per cent in 15,799 cases of early syphilis, while Goldstein[9] found 20 in 7462 patients with early syphilis (0.26 per cent). We found but 2 cases of jaundice in 1065 early cases of syphilis (incidence of 0.18 per cent).

Post-arsphenamin Jaundice. Statistics on the frequency of jaundice in syphilis following treatment with one of the arsenobenzenes presents a strikingly different picture. Of the 10,021 cases of syphilis examined in the clinic during the period, only 4126 were treated in our clinic with one of the arsphenamins. The remainder were sent back to their home physicians for treatment or for various reasons were treated with heavy metals and iodids or plasmodium therapy. Our patients received a total of 35,936 treatments and 56 developed jaundice (1.35 per cent). A comparison with other reports shows this to be about average. For example, Harrison[10] had an incidence of 0.6 per cent; Gaston and Poutoiseau,[11] in 1600 patients, 0.76 per cent; Stokes, Ruedemann and Lemon,[12] in 5200 patients, 1.3 per cent. On the other hand, Scott and Pearson[4] reported 1.7 per cent; Pulvermacher,[5] 2.75 per cent; Friedmann,[13] nearly 3 per cent; Clément-Simon and Vulliémoz,[14] in 1100 patients, 5 per cent. In our groups, then, post-arsphenamin jaundice is 7.5 times as frequent as pre-therapeutic jaundice.

The material on which this part of our study is based consists of 65 consecutive cases of jaundice following one of the arsenobenzene preparations. The group ranged in age from 10 to 58 years (average, 30.6). There were 26 women and 39 men, or 1 to 1.5, while in the treated group the women outnumbered men by 1.27 to 1. The duration of the syphilitic infection ranged from a few weeks in early cases to periods of 15 to 25 years in late cases. All types of syphilis were represented, and in 3 of the cases treated elsewhere syphilis was proven to be non-existent. At the time treatment was instituted, 7 patients had only a primary lesion, 12 had developed secondary manifestations, 22 were latent, 14 had central nervous system syphilis, 2 had aortitis, and 5 had congenital syphilis. The greatest interest attaches as to which type of arsphenamin is the most hepatotoxic. (Table 3.)

Table 3.—Incidence of Jaundice According to Drug and Method of Treatment.

	No. of cases treated.	No. of cases jaundice.	Percentage incidence.
Tryparsamid	279	3	1.07
Neoarsphenamin	921	7	0.76
Arsphenamin	2926	46	1.57
Non-intensively (weekly)	563	10	1.77
Semi-intensively (3 in 10 days)	363	5	1.39
Intensively (3 in 3 days)	2000	31	1.55
Totals	4126	56*	1.35

* Nine other cases came to hospital because of jaundice following arsenobenzene. All treated by neoarsphenamin.

It will be noticed that arsphenamin, calculated on a percentage basis, produces twice as many cases of jaundice as neoarsphenamin. This, however, probably does not indicate that neoarsphenamin is less hepatotoxic, as most of the patients treated with this drug are babies and children with congenital syphilis, in which group we had no case of post-arsphenamin jaundice below the age of 10 years. Moreover, all the outside cases entering the hospital for jaundice had received neoarsphenamin. It will also be noted that the intensive method of administering arsphenamin (3 treatments in 3 days) has not produced a greater percentage of jaundice than the less intensive methods. We also found no relation between the severity of the jaundice or its duration and the amount of drug given. That impurities or a deteriorated drug could be responsible in many cases does not seem likely when the cases are well distributed over several years. Obviously, however, such a complex unstable drug might contain impurities and be responsible in a few cases. (See Wilcox.[15]) In 1928 we changed, following a fatal case of arsphenamin jaundice, to the preparations of another firm, since when we have had no fatal cases from jaundice, but we have had more cases.

Cases of post-arsphenamin jaundice can definitely be separated into early and late types. In the early cases the jaundice may follow treatment in from 1 to 15 days. Clément-Simon and Vulliémoz[14] have reported the earliest case, which came on immediately following the first injection which had caused a nitritoid crisis. In our series, 18 are early cases (average, 6.5 days from last intravenous treatment).

The causes ascribed to early icterus may be listed as follows: (1) Herxheimer reactions. (2) Toxic reactions: (*a*) due to overdosage; (*b*) due to hypersusceptibility or idiosyncrasy.

The first of these conditions, the Jarisch-Herxheimer reaction, or "reaction de foyer" of the French, has long been recognized as a cause of early benign and fairly transient jaundice. The mechanism is due to a sudden destruction of spirochetes in the liver and elsewhere, with a liberation of syphilotoxin and subsequent damage to the liver. Two of our early cases we feel were the result of this phenomenon. They came on within 24 hours after the first injection in patients who had early syphilis but had had no previous treatment. The jaundice was mild and lasted but 4 or 5 days. Later the patients were again placed on an arsphenamin, without further trouble.

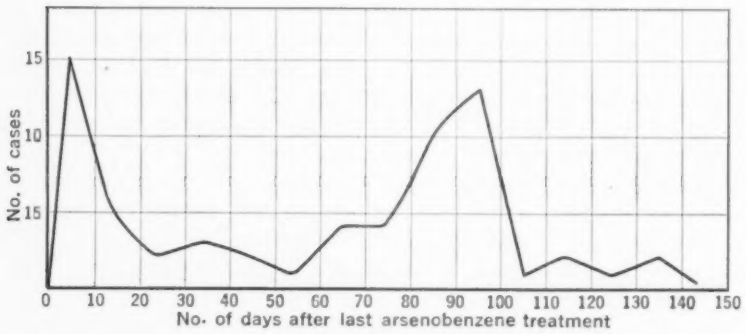
Excessive dosage can, we feel, be responsible for but 1 of our cases. The patient, a man, aged 58, was given a pre-operative course of 2 neoarsphenamin treatments in our clinic. Upon discharge from the hospital he received at the hands of another physician 16 intravenous injections of neoarsphenamin, given twice a week. Jaundice followed the last injection by 3 days. Although this patient also had avertin anesthesia and was a chronic alcoholic,

we feel that he also received an excessive amount of neoarsphenamin for his age and condition.

In the remaining 15 early cases the dosage of drug was not excessive and was less than that ordinarily given. The average number of treatments was 2.6 per patient. In this group in all cases there are initial signs of toxicity which followed the administration of the drug immediately or within a few hours. Most commonly this consists in a febrile reaction, frequently initiated by a chill and accompanied by a marked gastro-intestinal reaction which may last for several days. A third of these cases developed a toxic erythema which subsided as the jaundice appeared. There is then a very definite trend of events leading from the time of treatment up to the onset of jaundice. That this is the result of a toxic reaction from arsphenamin is self-evident.

Late Post-arsphenamin Jaundice. It is in late icterus following therapy that the difficulty in diagnosis obtains. Here the widest divergence of opinion exists, and it is in this group that a majority

TABLE 4.—OCCURRENCE OF JAUNDICE FOLLOWING LAST ARSENOBENZENE TREATMENT.



Number of cases of jaundice occurring in first 2 weeks, 20 (30 per cent); in first 2 months, 28 (43 per cent); after first 2 months, 37 (57 per cent).

of our cases fall. On the average, these patients complete 6 intravenous treatments and have been discharged on heavy metal for a period of 3 months. It is just at the time when they are due to continue their third course of intravenous treatment that their jaundice appears. Table 3 shows the rise of this second or late peak of jaundice; nearly $\frac{2}{3}$ of our cases occur at this period. On the average, it occurs 80 days after the last intravenous treatment, the height of the curve falling at 96 days. Our longest delayed case is 139 days.

There are three major theories as to the cause of the late icterus: (1) Delayed toxic action of arsphenamin on the liver; (2) a hepatorecurrence; and (3) an intercurrent infection, usually in the nature

of a so-called catarrhal jaundice. Numerous other factors have been emphasized by various investigators at least as contributing elements: heavy metals, alcohol, malaria, pregnancy and many others.

The delayed toxic action theory, which was at first the favorite, has some evidential support. Table 3 shows that there is a fairly definite silent period of about 3 months after administration of the drug. This interval, which we can refer to as the "latent period of jaundice," is well marked and is noted both in our series and in those of other clinics.[12, 16] Todd[17] reported an average latent period of 10 weeks. He also reported that further administration of neoarsphenamin had a deleterious effect upon the course of the jaundice and concluded, therefore, that the drug was a causative factor. Against this view we can summon certain experimental evidence, namely, the frequent failure to produce arsphenamin jaundice in laboratory animals, even with definitely toxic doses.[20]

Certain investigators have reported that arsenic is retained in the liver for months.[18, 19] Silbergleit and Föckler,[20] on the other hand, were unable to show arsenic in the liver of 2 fatal cases, nor could they demonstrate arsenic in the excretions. Lynch and Hoge[21] likewise failed to demonstrate arsenic in 3 fatal cases. Most clinicians have been unable to find arsenic in the urine and hair of the late jaundice cases. A majority of our determinations have been negative, and 2 of 3 positive tests were obtained within 1 week of the last treatment. One of our late cases gave a positive test for arsenic 104 days after the last treatment. No studies of arsenic in feces of jaundice patients have been made. The greatest variations in opinions exist as to the duration of arsenic retention and excretion following arsphenamin. (See Vogel.[22]) Milian[23] found, in a patient dying from syphilitic meningitis after 3 injections of arsphenamin, that the lungs and spleen contain several times more arsenic in proportion to their weight than the liver, indicating that the liver is not a site of election.

It is incontestable, however, that arsenic jaundice is much more frequent than jaundice in the population as a whole. Ruge[24] found jaundice to occur 16 times more frequently among the personnel of the German Navy treated with salvarsan than among the rest of the Navy—an excellent control as the two groups lived under the same environment. Without doubt arsphenamin plays a major part in the production of the late jaundice, but the exact mechanism of its action is not clear. The ability of patients again to tolerate arsphenamin after recovery from a late jaundice is well known, and 16 per cent of our patients later continued arsenobenzene therapy either in our clinic or elsewhere without a single recurrence of jaundice. There must be, then, some immediate factor which precipitates the hepatitis.

The rôle of syphilis as a cause of the late jaundice has long been

championed by Milian,[25] who advanced the theory that in 90 per cent or more of the late cases the jaundice was the result of a recurrence of syphilis in the liver. In other words, it was a hepatorecurrence comparable to mucocutaneous relapse and the well-known neurorecurrence. He based his opinion on the time interval which occurs between the last injection of the drug and the onset of the jaundice, noted the case as being due to short and inadequate treatment, and recommended further intensive treatment with arsphenamin. Of 75 cases so treated, 60 had good results, 11 were intolerant to arsenobenzenes, and there were 4 deaths. The duration of the jaundice was shortened to 10 or 15 days, according to his reports. This latter fact has not been observed in other clinics when arsphenamin has been given.

Let us enumerate first the evidence favoring hepatorecurrence: (1) The time interval between the last arsenobenzene and the onset of jaundice tends to average about 3 months, and this corresponds with a period in which neurorecurrence or mucocutaneous relapse may occur. (2) Patients frequently discontinue their heavy metal therapy during this period and are predisposed to relapse. (3) Administration of further arsphenamin during the jaundice has not resulted in any severe exacerbation of the jaundice or symptoms, and frequently causes no difficulty; this would be unusual if arsphenamin were the cause of the liver dysfunction. (4) Late icterus is infrequently accompanied by symptoms of arsphenamin intoxication. (5) Finally, Milian frequently finds concomitant evidence of active syphilis and a high percentage of positive serologic reactions. Others have reported jaundice associated with recurrent secondary lesions.[27]

As opposed to this view, the following facts stand out: (1) In 42 cases of late jaundice there was not a single case of mucocutaneous relapse or neurorecurrence, yet a recent survey indicates that with early syphilis we have about 4 per cent neurorecurrences during the first year of treatment. (2) Only 14 of the 45 jaundice cases had had active syphilis, 15 cases were purely latent, 12 had central nervous system syphilis, 2 congenital syphilis, and 1 had aortitis. In these latter groups an active relapse would be unusual. (3) Twenty-five of the patients had 6 or more 2-grain injections of bismuth subsalicylate or 40 mercury rubs following the last arsphenamin injection, 18 patients had less than this amount, and only 2 had no heavy metal therapy during the interval. All of the patients had received bismuth injections along with the intravenous therapy. We believe this adequate to prevent relapse in most cases. (4) The serologic reaction remained unchanged in 19 patients of the group, 11 patients did not have serologic study, 7 patients had serologic tests during the time of jaundice and only 2 were positive. Eight other patients had a negative serologic reaction after the jaundice. There were no reversals from negative to positive with the onset of

jaundice. (5) Five cases in whom slight jaundice was present, but not noted, returned to the clinic and were inadvertently placed on arsphenamin. Of this group following the next arsenical treatment, 1 patient died in 5 days, the only death from treatment on our service during the period studied. The other 4 recovered from their jaundice in an average of 23 days. This recovery in 4 of the cases is not sufficient evidence to justify a diagnosis of syphilitic jaundice. We feel that they recovered in spite of the treatment rather than because of it. (6) In this controversy it is of greatest significance to note that no known form of liver syphilis is commonly characterized by icterus and in our 91 cases of hepatic syphilis only 16 were jaundiced.

The third major problem in this discussion concerns itself with the differentiation of delayed post-arsphenamin jaundice from jaundice due to infectious hepatitis. The latter is often termed epidemic jaundice when it occurs in large numbers, or "catarrhal" jaundice when it occurs sporadically. This type of jaundice has always been common in troops during wars. A marked increase was noted during the latter part of the World War and in the following years epidemics were reported in Europe and North America. Stokes, Ruedemann and Lemon[12] noted an increase in their post-arsphenamin jaundice simultaneously with an epidemic of jaundice in southern Minnesota. More recently Ruge has published a series of statistical articles on the incidence of post-arsphenamin and infectious jaundice in the German Navy.[24, 27] In support of this view the strongest point is the almost complete inability in any given case to make the differential diagnosis between infectious and toxic hepatitis. As an aid in study of this phase of the condition, we have taken 69 consecutive cases of infectious jaundice which occurred during a similar period. They represent sporadic cases of infectious hepatitis and they vary more in their symptoms and physical findings than is the case where the infection occurs in epidemic form.

The patients in this group range in age from 1 to 60 years, the greatest number falling in the second and third decades, and the average age being 25 years. There were 25 female and 44 male patients. Six cases of post-arsphenamin jaundice were found diagnosed "catarrhal" jaundice and 2 cases of untreated syphilis with jaundice were found in the group. These, together with those cases which were later found to have stone or cholecystitis, were excluded for the purposes of comparison with our post-arsphenamin group. Surgical cases were likewise excluded in the post-arsphenamin group. Milian, in a recent article,[23] claims that quiescent angiocholitis and cholelithiasis are often stirred into activity by antiluetic treatment. We have not gained this impression.

The average number of treatments with arsphenamin or similar drug in the late jaundice is 6 injections, and the highest total

dosage given in 6 treatments was 3.6 gm., while for the average the total dosage was 2.4 gm. With neoarsphenamin the figures are similar. The patients did not develop any immediate reaction of severity nor have any previous difficulty until the onset of jaundice. This lack of toxic symptoms at the onset favors the opinion that other causes than arsphenamin play the immediate rôle in the production of the late icterus. The average case has its onset at about the time when the patient is due to return for continuation of arsphenamin therapy. It frequently follows an upper respiratory infection or gastro-intestinal upset, after which the patient feels ill and in many of the cases nausea and vomiting ensue. The appetite becomes poor, there is a loss of weight, and a lack of energy. Then, in about 6 to 8 days his friends notice he is becoming jaundiced. Usually by the time he returns to the clinic the jaundice is well marked, but the patient is feeling somewhat better. Under treatment in the hospital the jaundice usually lasts a month, fading very slowly. Table 5 compares the symptoms in our post-arsphenamin and infectious groups.

TABLE 5.—COMPARISON OF SYMPTOMS IN POST-ARSPHENAMIN AND INFECTIOUS JAUNDICE.

	Post-arsphenamin jaundice, per cent.	Infectious jaundice, per cent.
Nausea	47.1	47.8
Vomiting	45.2	39.1
Asymptomatic	24.5	7.3
Pain or soreness of abdomen	20.7	34.3
Upper respiratory infection	20.7	18.9
Fever	17.0	21.7
Anorexia	17.0	39.1
Indigestion, distress, "gas," etc.	13.2	34.3
Chills	11.3	8.7
Pains in back or extremities	9.4	8.7
Pruritus	9.4	8.7
Constipation	7.5	26.0
Diarrhea	7.5	1.4
Malaise, weakness	5.6	31.8
Headaches	1.9	13.0
Epistaxis	1.9	1.4

The essential differences noted between the two groups are: (1) Asymptomatic onset and course are more common in the post-arsphenamin group. (2) Pain or tenderness in the abdomen is a bit more common in the infectious group, as are headache, malaise and weakness. (3) Constipation is more common and diarrhea uncommon in the infectious group. (4) Indigestion and loss of appetite are more common also in the infectious group. Other writers have pointed out that the patient with therapeutic jaundice is a sicker patient than with infectious jaundice, a point that our experience does not cover. Other than the evident icterus, which is of varying degree, the most significant physical finding in both groups is a palpable liver. The liver is more commonly tender in

infectious jaundice, while a palpable spleen is a bit more common in the post-arsphenamin group.

TABLE 6.—PHYSICAL FINDINGS IN POST-ARSPHENAMIN AND INFECTIOUS JAUNDICE.

	Post-arsphenamin jaundice, per cent.	Infectious jaundice, per cent.
Palpable liver	60.0	53.6
Liver tenderness	13.7	26.1
Palpable liver and spleen	11.6	5.8
Excoriations	0	2.9

Although certain differences in the two groups are evident, it is, nevertheless, apparent that in any given case it is quite impossible to differentiate between them. Numerous studies have been made on the two conditions with the purpose of aiding in a differential diagnosis, but material differences are not consistently found. Stool and urine examinations or a history of clay-colored stool or dark urine gave results which were approximately the same. The findings depend more upon the time, severity and duration of the jaundice than upon any other factor. Leucin and tyrosin crystals were found in the urine of a patient who died with acute yellow atrophy and in another patient who subsequently recovered.

Several investigators have studied the blood findings and arrived at opposite opinions as to their value in differential diagnosis and significance. Ruge[28] has studied his cases and concluded that there is no difference between the blood counts in post-arsphenamin and infectious jaundice. He found in both conditions an early mild leukocytosis with an increase in neutrophils which soon gives way to a mild leukopenia with a lymphocytosis and mononucleosis. With Schilling counts there was no shift to the right or left. Thewlis and Middleton[29] had previously reported leukopenia as "an almost constant blood finding in uncomplicated catarrhal cholangitis." Polymorphonuclear cells were depressed more than the other white blood cells, and the large mononuclear cells show a slight increase. They further reported the depression to be in direct ratio to the severity of the disease and that in the average case the blood returns to normal in about 2 weeks. Still earlier, Jones and Minot[30] reported a transient and minor leukocytosis and a constant absolute lymphocytosis even when leukopenia was present. Lerman[16] studied a group of 50 cases of arsphenamin jaundice statistically and concluded that "arsphenamin jaundice was characterized by a slight leukocytosis and a normal differential count in contradistinction to the characteristic leukopenia with relative lymphocytosis that develops in catarrhal jaundice." Furthermore, the total leukocyte count in arsphenamin jaundice tends to be higher during the first week of jaundice than thereafter.

Compiling the reports from our blood counts, we have the results indicated in Table 7. This method in arriving at an average blood

picture has many sources of error and it is not surprising that different investigations have resulted in a wide divergence of opinion. We are struck by the wide range of variation in the total leukocyte counts and in the differential pictures and were unable to correlate these findings either with the day of the disease or its severity.

TABLE 7.—RESULTS OF BLOOD STUDIES IN INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE.

	Infectious jaundice.	Post-arsphenamin jaundice.
Average leukocyte count before onset of jaundice . .	5715 (60 per cent polymorphonuclear cells)	6550 (71 per cent polymorphonuclear cells).
Average leukocyte count after onset of jaundice . .	8357 (61 per cent polymorphonuclear cells)	7066 (61 per cent polymorphonuclear cells).

NOTE.—The period before onset of jaundice varied from 1 to 11 days in the two groups and the period after jaundice varies from 1 to 54 days. They represent, therefore, early and late periods respectively in the duration of the disease.

In our opinion, the blood study will not aid in the differential diagnosis. Blumer[31] has stated that the blood picture of infectious jaundice is not characteristic but variable. With this opinion we are in entire accord, and we feel that this is equally true in the group of post-arsphenamin cases. There is to date no satisfactory clinical or laboratory method of distinguishing between certain cases of post-arsphenamin jaundice and others of infectious jaundice.

Table 8 shows a tendency for the late post-arsphenamin jaundice cases to be slightly more common during the winter months, but this is not so marked as with infectious jaundice. This tendency has been previously noted by others. Todd,[17] reporting a series of cases which occurred during the World War, found that the greatest majority of his cases started with the onset of cold weather.

TABLE 8.—COMPARING INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE ACCORDING TO MONTHLY OCCURRENCE.

	Jan.	Feb.	Mar.	April.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
Infectious Jaundice (69 *Cases*).	4	7	6	4	2	6	4	4	5	9	8	10
Late Post-arsphenamin Jaundice (45 *Cases*).	7	7	2	2	4	1	3	3	4	3	4	5

In Table 9, comparing yearly incidence of post-arsphenamin and infectious jaundice, it can be pointed out that nearly 60 per

TABLE 9.—YEARLY OCCURRENCE OF INFECTIOUS AND POST-ARSPHENAMIN JAUNDICE FROM 1925 TO 1933.

	1925.	1926.	1927.	1928.	1929	1930.	1931.	1932.	1933.*
Infectious Jaundice (69 *Cases*).	4	8	12	4	10	11	14	8	0
Late Post-arsphenamin Jaundice (45 *Cases*).	1	3	4	6	3	5	13	8	2

* January and February only.

cent of our late post-arsphenamin jaundice cases occurred during the years of 1930, 1931 and 1932. At the same time, just a few (less than half) of the cases of infectious jaundice were treated in the hospital. An even greater tendency for such a grouping has been reported by writers who have studied the problem during an epidemic of acute infectious jaundice (Ruge, Stokes and others).

These figures we feel are of some significance in spite of the fact that the groups studied are not well controlled. If post-arsphenamin jaundice were identical with infectious jaundice, we would expect the incidence to be similar, and we would have but 6 instead of 45 late cases. It is evident, then, that too much significance cannot be placed on the above comparison. In a review of the occurrence of infectious jaundice in the student group of the University, the rate per M averaged 1.55 over the period of 8 years, from 1925 to 1933. In the student group, cases of infectious hepatitis varied from 2 in 1928–1929 to 24 in 1932–1933, with an average enrollment of 8000.[33]

Other possible contributing factors can be considered. What part does heavy metal therapy play? Ruge[24] found only a few cases following the administration of bismuth alone, but he does not state how many cases have been so treated. In the opinion of Silbergleit and Föckler,[20] who reported 13 fatal cases, the simultaneous administration of the heavy metal with arsphenamin is much more productive of serious accidents. Strathey, Smith and Hannah[33] offer the same opinion. In our experience, neither bismuth nor mercury alone have produced toxic jaundice, and it has long been our practice to limit the treatment of cardiac and hepatic cases of syphilis to heavy metals and iodids, and not to treat with the arsphenamins patients over the age of 50 years who have only latent syphilis, except in a few cases. We have given or advised such treatment in a large number of individuals with never a case of toxic jaundice. We are consequently of the opinion that the heavy metals are not especially hepatotoxic, but this, of course, does not prove that they do not play a contributing rôle. We have 6 cases in our late jaundice group who developed a stomatitis after using mercury rubs before the onset of their toxic hepatitis. There were no cases with diarrhea or renal damage from mercury in this group. Furthermore, none of our patients who have had a nephrosis from mercury has subsequently developed jaundice. We have had no untoward reactions with bismuth. One patient, a non-syphilitic with a phagedenic ulceration of the penis, was treated elsewhere with a series of 50 injections of bismuth antimony tartrate and later was given 2 injections of neoarsphenamin. He developed a jaundice 7 days after the last intravenous injection and entered the University Hospital for treatment. Keefer[34] has reported toxic jaundice following the administration of antimony preparations.

Several writers, during and immediately following the World

War, believed that the increased incidence of jaundice at that time was the result of a very limited diet which predisposed the liver to damage by arsphenamin. We do not consider that such a factor applies in our cases. A considerable number believe that a high carbohydrate intake spares the liver and they recommend such a diet for the treatment of toxic hepatitis.

We believe, however, that the condition of the organ does play an important rôle in the production of the jaundice either of the early or late type. That the syphilitic infection itself imposes some load upon the organ cannot be denied. In any systemic infection it must be called upon in some respect in protecting the organism and eliminating the endogenous toxins. Rehder and Beckman[35] have stressed the point that the stage of infection with syphilis is important and that jaundice is more common with a florid secondary syphilis of some months' duration, and less common in early primary cases and late central nervous system syphilis. They point out that jaundice is not a common complication of antisyphilitic therapy in psychopathic institutions where late or old cases of syphilis predominate. Zimmern[36] is also of this opinion and in his collected cases jaundice occurred in early syphilis 218 times as compared with 88 cases in late syphilis. Our records do not bear out this contention directly—19 of our cases were either in the primary or secondary stage, 22 were purely latent, 14 had nervous system syphilis, and 5 were cases of congenital syphilis.

Other evidence of recent or concurrent liver damage is indicated in Table 10. One-third of the cases had, in addition to the syphilis and the arsphenamin, other causes which may have contributed to the failure of liver function.

TABLE 10.—EVIDENCE OF PREVIOUS LIVER DAMAGE IN 65 CASES OF POST-ARSPHENAMIN JAUNDICE.

	Cases.	Percentage incidence.
Hepatic disease	9	13.8
Specific hepatitis	3	
Gall-bladder disease	4	
Previous jaundice	2	
Malaria	4	6.1
Recent pregnancy	4	6.1
Recent general anesthesia (Avertin-ethylene-ether)	3	4.6
Alcoholism	2 (?)	3.1
Percentage of patients with evidence of previous liver damage		33.7

The data in Table 10 constitute only presumptive evidence of liver damage, which in the absence of satisfactory tests for liver function is as yet unproved. This, of course, does not include any estimate of occult syphilis of the liver: in all cases where syphilis existed, some damage may have been done.

Intercurrent infection other than infectious hepatitis probably plays some part in the production of jaundice. Keefer[34] is of the

opinion that streptococcal infection may produce profound anatomic changes in the liver and account for a jaundice in patients with streptococcus septicemia. Upper respiratory infections were noted in the records of 13 of our patients, oral sepsis in 20, otitis media, sinusitis or tonsillitis in 10 more, mercurial stomatitis in 6, and a severe pyelitis in 1.

In addition to infections, 3 of the group had had a general anesthesia following the course of antiluetic therapy. Jaundice and acute yellow atrophy of the liver following chloroform are not rare. This has been the subject of experiment by McJunkin,[37] who reported experimental failure to damage the liver of animals with arsphenamin after it had already been affected by chloroform. Jaundice following both avertin and ether have been reported.

The part played by pregnancy and by alcoholism is still more difficult to evaluate, but since both are known to cause liver damage under certain conditions they cannot be considered as of no consequence. Alcoholism has been singled out as a contributing factor in producing the jaundice by several who have commented on the subject. A history of alcoholism was obtained in but 2 of our cases.

Jaundice in Therapeutic Malaria. Since jaundice not infrequently occurs during or shortly following malarial therapy in syphilitic patients, we have reviewed these cases in the hope that it might throw some light upon our problem. That jaundice occurs as a complication of malaria has long been recognized, and Clifford[38] states that malaria always damages the liver, sometimes fatally. Cirrhosis of the liver with pigment formation in chronic malaria forms one of the classic pictures in human pathology,[39] even though it is uncommon. James, Nicol and Schute[40] record jaundice as a very frequent complication of induced malignant malaria using P. falciparum.

We have treated 322 patients with plasmodium therapy for syphilis of the central nervous system of various types. Out of this number, 7 (2.14 per cent) developed jaundice. Only 1 of these patients had previously had a jaundice following arsphenamin. In this patient the course, symptoms and severity of the jaundice were almost identical during both attacks. We have had 5 other cases of post-arsphenamin jaundice who subsequently were treated with malaria and who did not develop icterus.

Three of the patients in this group of 7 had never had arsenobenzene therapy of any type and 3 had had recent treatment. In 1 case the interval following the last intravenous treatment was just 76 days, the same as the average in our late type of cases. Two patients who received malarial therapy before arsphenamin treatment developed jaundice during their initial course of arsphenamin. We can draw no conclusions except that combined malaria and arsphenamin, both exerting a toxic action on the liver, lead to a jaundice more frequently than either agent alone. There is nothing characteristic in the course of jaundice in malaria which

aids in differentiating it from infectious or toxic icterus. The van den Bergh reaction is indirect when the bilirubin is lower than 20 mg. per 1000 cc. and direct usually when above this figure. Few fragility tests have been made. Anemia has with some strains of the plasmodium been severe enough to warrant cessation of the paroxysms. At other times the hemoglobin and red blood cell count have remained higher than the appearance of the patient would indicate. We agree with the opinion expressed by O'Leary, Green and Rowntree,[7] that hemolytic crises may in part explain the jaundice of mild degree, but that when severe there is an element of hepatic injury. Until this hepatic damage occurs, the blood bilirubin, although elevated, does not usually produce a clinical jaundice.

During the past few years we have made blood bilirubin determinations on all of our jaundice cases about every third or fourth day. The van den Bergh reaction, as pointed out above, varied with the quantity of bilirubin, almost always being direct when the bilirubin was high and indirect when low, that is, below 20 mg. per 1000 cc. One case with Banti's syndrome gave biphasic reactions with a reading as high as 42 mg. per 1000 cc. The highest bilirubin obtained in the infectious jaundice group was 120 mg. per 1000 cc. and the duration of jaundice in this case was 28 days, with recovery. The highest reading in the post-arsphenamin group was 100 mg. per 1000 cc. and the patient recovered in 31 days. In general, when the blood bilirubin is higher than 50 mg. the duration of the jaundice is longer than a month and often 2 months. The jaundice recedes slowly and this is said to be indicative of widespread liver damage. When the jaundice does not become intense, and the blood bilirubin is but 20 to 25 mg. per 1000 cc., the duration is from 1 to 3 weeks. There is considerable variation in this matter. In our 2 fatal cases the highest readings were 70 and 94 mg. per 1000 cc. Noticeable variations in the depth of jaundice are accompanied by a corresponding rise or fall in the bilirubin reading. At the onset the bilirubin content of the blood rises faster than the depth of the icterus would indicate, while later the icteric tint may not fade as rapidly as the bilirubin content of the blood falls.

Milian[23] reported positive blood reactions in his late cases, while others have reported an unusual number of negative serologic reactions. Rehder and Beckman[35] reported that 20 of their patients had negative serologic reactions before the onset of icterus, and during the period of jaundice he had only 3 with positive reactions, and these 3 patients did not subsequently show serologic reversal. Strathey, Smith and Hannah[33] reported 8 fatal cases and 39 nonfatal cases in which all but 2 gave a negative Wassermann reaction before their jaundice cleared up. Todd[17] found a negative Wassermann in all 24 of his cases during jaundice. In the last two groups the patients were British troops and all were cases of early syphilis.

In our cases with both early and late jaundice covering both

recent and old syphilis, we were also struck with the unusually high percentage of reversal of the serologic test from positive to negative. We consider this unusual in view of the relatively small amount of specific therapy—2 to 8 treatments—and the short period which elapsed from the start of treatment, averaging but 3 months. Of 65 cases, 57 were serologically positive on admission to the hospital, and 40 of these had further serologic study. Thirteen had blood tests during the period of jaundice; 3 of these had become negative, 4 were less strongly positive and 6 remained unchanged. Of 33 cases which have returned to the clinic, 18 are still positive while 15 have been persistently negative. Of the 15 cases showing reversal, 8 were of early syphilis, 4 were purely latent cases, and 3 had central nervous system syphilis. None of these patients have again become positive and several of them have been followed for 6 years. Of those in whom there were no change from positive to negative, 3 were cases of early syphilis, 5 were latent, 2 had aortitis, 7 had central nervous system syphilis, and 1 had congenital syphilis. A more comprehensive study of the cases in which serologic reversal occurred will be reported in a later paper.

We had only 2 fatal cases and 1 of these had not received his treatment at our hands. We have had, then, but 1 death from toxic hepatitis in 4126 cases. The patient treated elsewhere received neoarsphenamin of a dosage not known. He had received several previous treatments with no apparent trouble. When after a period of 6 months he resumed treatment, he was sick following the injection and developed jaundice on the 11th day. He died 36 days later with toxic nephritis and a terminal bronchopneumonia. The liver had shrunken in size before death and postmortem examination showed acute yellow atrophy of the liver. The second patient was treated with arsphenamin and had received 8 treatments, with a total dosage of 3.35 gm. As has been pointed out above, the patient was given more arsphenamin at a time when he had bile in his blood. This patient's jaundice evidently was the result of a previous course of treatment which had been completed 91 days before. He became markedly icteric, irrational, then comatose and died within 5 days. The autopsy examination showed acute yellow atrophy of the liver. This experience leads us to advise strongly against the use of any arsphenamin preparation in patients with jaundice. If there is any evidence suggesting hepatorecurrence, heavy metal treatment would be the method of choice.

Summary. The subject of post-therapeutic jaundice as seen in our clinic during the past 8 years had been discussed. A review of several groups of patients was made with particular reference to the incidence of infectious jaundice and of other associated factors which, together with the type of treatment administered, could have led to liver damage. An analysis has been made with reference to the frequency of icterus following arsenobenzene and associated heavy metal therapy. This group was further studied with

reference to the type of arsenobenzene drug employed and an effort to determine their relative hepatotoxicity made. Studies have been made as to the incidence of icterus occurring as a manifestation of syphilis in cases in which arsenobenzene had not been employed. This was undertaken for the purpose of comparison with the post-therapeutic group and tends to incriminate the arsphenamins as factors in the production of jaundice. Symptomatology and physical findings have been studied in an endeavor to determine, if possible, the pathognomonic criteria for post-arsphenamin jaundice.

Conclusions. 1. Jaundice following the use of arsenobenzenes in the treatment of syphilis is a not infrequent complication, and its relative incidence in our series and in those reported by others indicates that a high degree of hepatotoxicity is exerted by the drugs.

2. The low incidence of jaundice in untreated syphilis, 0.18 per cent, as compared with a percentage of 1.37 following arsphenamin, further incriminates these drugs as factors.

3. It is not believed that post-therapeutic jaundice can be regarded as a hepatorecurrence, as is stated by Milian.

4. The symptomatology and the physical findings of the late or delayed type of post-therapeutic jaundice so closely approach those of infectious or so-called catarrhal jaundice as to make differential diagnosis possible only upon the history. The blood findings are not constant or characteristic.

5. A possible relation of post-arsphenamin jaundice to the incidence of infectious jaundice, as pointed out by Stokes, Ruedemann and Lemon, is to some extent borne out by our studies.

6. About 60 per cent of the cases of post-therapeutic jaundice occurred in a period of 3 years, during which time almost half of the cases of infectious jaundice studied for comparison also occurred.

7. Extraneous associated factors exerting hepatotoxicity, such as pregnancy, malaria and alcoholism, play a minor rôle.

8. The pathologic diagnosis of acute yellow atrophy in 2 fatal cases studied, as well as others reported in the literature, indicate that the icterus results from a severe intoxication and destruction of the liver substance analogous to other forms of poisoning leading to acute yellow atrophy.

9. Until more accurate means are at hand to determine susceptibility and liver function, and until the drug is modified to make it less hepatotoxic, post-arsphenamin jaundice will continue to be among the severe complications of the modern treatment of syphilis.

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THERAPEUTIC PNEUMOTHORAX IN EXPERIMENTAL LOBAR PNEUMONIA IN DOGS.*

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Therapeutic pneumothorax on the affected side in lobar pneumonia has been used by Continental clinicians since 1921, when

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Friedmann[1] reported on its use in 7 patients. He found that when artificial pneumothorax was instituted on the affected side severe pain subsided and respirations became quiet, with evident improvement in the general condition. In these and David's[2] 6 cases all patients recovered without complications. Schottky[3] (1923) reported using the procedure once "as a last resort" on the 5th day of the disease with excellent results and prompt convalescence. Ibraham and Duken[4] (1928) used it in 3 infants with pneumonia with recovery; and Duken[5] later successfully treated 5 other children with pneumonia by this method. Jahr and Neumann[6] also reported 5 cases of lobar pneumonia in infants successfully treated. The cases reported by Ibraham and Duken, and Duken, as well as one reported by Jahr and Neumann, were treated late in the disease (12th to 35th day); here the treatment must be regarded as being given for a complication of lobar pneumonia rather than for the acute pneumonia itself. In 1931, Taylor[7] used artificial pneumothorax in the treatment of pleurisy in pneumonia in 3 cases, with immediate relief of pain. In 1932, Coghlan[8] used it in 6 cases of lobar pneumonia with complete recovery in 5. In the 1 fatal case, an attempt was made to produce an immediate and complete crisis because of the desperate condition of the patient; 750 cc. of air was injected at one time, a very violent crisis set in, the patient perspired freely and cyanosis became markedly diminished. A few hours later the pulse began to rise and signs of failure of the right ventricle appeared, the patient dying the next day. He says "the fatality in this case can be attributed to an error in judgment in a difficult situation and lack of knowledge of the technique, owing to inexperience, rather than to a defect in the method of treatment itself, for it was obvious that the pneumonic process was as well controlled by the artificial pneumothorax in this instance as in the other cases."

Coghlan's work has stimulated others to use this form of therapy and in the past year Hanau[9] and Guadarrama[10] have commented favorably on its uses in lobar pneumonia and the latter has published 1 case. Li[11] reported 6 cases from China with one fatality in a case that also had an effusion in the right pleural cavity. After the injection of air there was marked improvement in the patient's condition. Four days later the fluid increased with consequent displacement of the heart to the left, death occurring on the 4th day. Anderson[12] reported 3 cases with complete recovery. Perlroth and Topercer[13] treated 7 patients with one death. The fatality occurred in a chronic alcoholic with confluent bronchopneumonia and jaundice. We know of no cases in the American literature.

The number of published cases totals 50. Their ages range from 6 weeks to 62 years. In 41, the day of the disease on which therapeutic pneumothorax was instituted ranged from the second to the tenth. In the remainder, the treatment was begun so late in the disease that it must be looked upon as treatment for a postpneumonic complication. The average number of treatments in each case was two

TABLE 1.—DATA OF REPORTED LOBAR PNEUMONIA CASES TREATED WITH PNEUMOTHORAX.

Author.	Cases	Ages.	Involvement.	Average days of disease.	Average number of treatments.	Average amount of air.	Result.
Friedmann (1921)	7	20–39	L. L. L. (6); R. L. L. (1)	2.9	1.4	370 cc. (60–500)	All recovered.
David (1931)	6	4–39	R. L. L. (2); L. L. L. (1); R. Side (1); R. U. L. (2)	5	...	.....	All recovered.
Schottky (1923)	1	44	L. L. L.	5	1.0	400 cc.	Recovered.
Ibraham and Duken (1928)	3	10 mos. 36 mos.	R. U. L. (3); R. M. L. (1)	16	2.6	270 cc. (100–400)	All recovered.
Duken (1930)	5	8 wks.–2 yrs.	R. U. L. (2); L. L. L.? (1); R. Side (1)	22	6.0	250 cc. (150–350)	All recovered.
Jahr and Neumann (1930)	5	6 wks.–6 mos.	R. U. L. (3); L. L. L. (1); R. Side (1)	7	...	.....	All recovered.
Coghlan (1932)	6	9–55	R. M. L. (2); R. U. L. (1); R. L. L. (1); L. L. L. (1); R. Mid. and Basal Zones; R. Lower and Mid. Zones; Rt. Lobar Pneu.	3.8	1.8	336 cc. (100–750)	Five recovered; 1 died.
Li (1932)	6	8–62	L. U. L. (1); Pleural Effusion; R. M. L. (2); R. L. L. (2); R. Central	6.5	1.8	261 cc. (200–350)	Five recovered; 1 died.
Anderson (1932)	3	25	L. L. L. (1); R. U. L. (1); R. M. L. and R. L. L. (1)	5	3.0	422 cc. (400–600)	All recovered.
Guadarrama (1932)	1	37	Left side	3	2.0	375 cc. (350–400)	Recovered.
Perlroth and Topercer (1932)	7	18–55	L. U. L. (1); R. U. L. (1); R. L. L. (1); Bronchopneumonia; L. L. L. (3)	3.8	1.4	410 cc. (50–500)	Six recovered; 1 died.

and the average amount of air injected at each treatment was 400 cc. for adults. In the entire group, 47 patients recovered and 3 died.

All those who have used therapeutic pneumothorax for lobar pneumonia enthusiastically recommend it. They state that following the induction of pneumothorax there is prompt amelioration of the distressing symptoms and there is initiated a series of events almost indistinguishable from spontaneous crisis, with profuse perspiration and fall in temperature in a few hours. Relief of pain is immediate in those cases where pleurisy is present. The improvement is only temporary, however, for on the disappearance of the pulmonary compression all the initial symptoms return. When the compression is maintained for 48 hr. or more the pathologic process usually ends in a definite crisis and normal convalescence follows. In lobar pneumonia, the pleura apparently has an abnormally high absorptive power and to maintain compression for 48 hr. a refill of air is usually necessary in 12 to 18 hr. following the first treatment. In 1 case Coghlan[8] estimated the urinary chlorids and counted the leukocytes before and after the defervescence produced by the artificial pneumothorax. He found a rise of the urinary chlorids of 60% and a fall in the leukocyte count of over 25% less than 24 hr. thereafter.

Despite these almost incredible reports in the literature, we were unwilling to treat patients on this evidence alone, and decided to study the problem in animals. We have therefore conducted a series of experiments on dogs with a comparable, untreated, control group in order to observe in detail the course of lobar pneumonia treated with artificial pneumothorax.

Robertson and his coworkers[14] have shown in their studies on natural immunity that the pneumococcidal action of the blood of dogs is not much greater than that of the average human being. While they do not know definitely that this property has the same significance in the immunity of both species, they do have evidence that the pneumococcidal power of the blood parallels in general the species resistance to pneumococcus infection.[15,16]

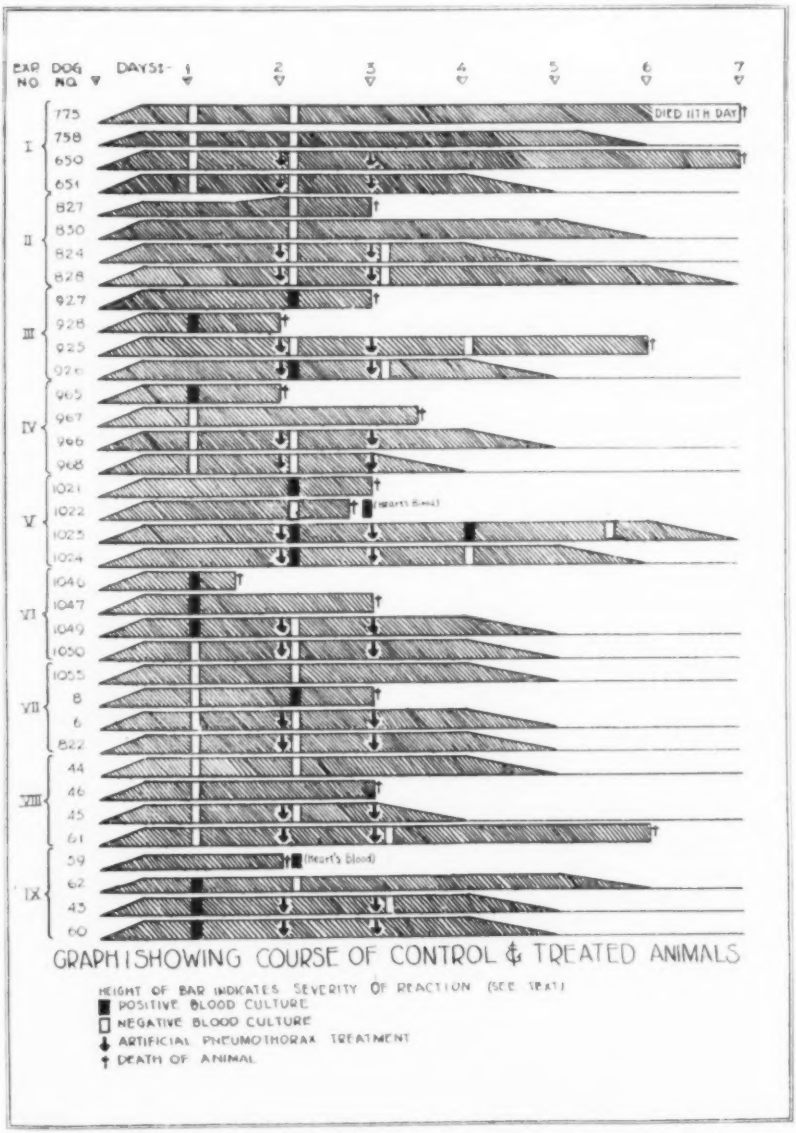
Method of Production of Lobar Pneumonia in Dogs. The method employed by us differed in a few details from that used by Robertson and his coworkers.[14] After anesthetization the dogs were bronchoscoped, a No. 8 F. soft rubber catheter was passed through the bronchoscope into the bronchus supplying the lower lobe of the lung desired, and 1 cc. of starch paste containing 0.06 cc. of sedimented, virulent pneumococci was injected through the catheter. Two syringe-barrels-full of air were then injected into the catheter to disperse the starch paste throughout the lobe of the lung supplied by that bronchus. The details of our technique were as follows:

1. *Dogs.* Healthy dogs, either male or female, of average weight of 10 kg. were used.

2. *Pneumococci.* Strains (Types 1 and 3) virulent for mice were used. These organisms were subjected to repeated passage through mice during the course of the study. All cultures used for inoculation were in the phase of active growth.

3. *The Starch-broth mixture* advocated by Robertson and his coworkers[14] was used.

4. *Anesthetization.* In order to obtain anesthesia with just enough relaxation necessary to permit bronchoscopy as well as the requisite fall in temperature for the establishment of pneumonia,[14] a preliminary injection of



morphin sulphate (6 mg. per kg. B.W.) was given. This was followed in 30 min. by the intraperitoneal injection of 15 mg. of sodium amytal per kg. body weight. About 15 min. after the injection of the sodium amytal, bronchoscopic instillation of the culture was made.

5. *Postanesthetic Care.* As the dogs had a subnormal temperature for several hours because of the anesthesia, they were placed on burlap bags in a warm room, lying on the side where the starch paste culture was introduced.

6. *After Care.* The dogs were allowed the liberty of their room and given daily one plentiful supply of cooked scraps and fresh water.

Experimental. Thirty-six dogs were used in groups of 4. Two dogs of each group were given pneumothorax and the other 2 were used as controls. Shortly after the injection of morphin there was a drop of between 3° and 4° F. in the temperature. On the day after the inoculation (*a*) with the starch-paste culture, the temperature was elevated and the dogs were acutely sick. They were usually too ill to walk and ate and drank very little. Physical signs of consolidation could be elicited. Unless treated by pneumothorax, the disease usually progressed and ended fatally on the 2d or 3d day. Of the 36 dogs in our series 14 developed demonstrable blood-stream invasion during life. In 2 additional animals the pneumococcus was recovered in the heart's blood postmortem. Of the 5 dogs which recovered without treatment, 1 had a positive blood culture. He recovered by crisis and was well on the 4th day.

TABLE 2.—DATA OF TREATED DOGS THAT RECOVERED.

Dog No.	Type pneu.	Involvement.	W.B.C. in thousands.	Temperature.	Blood culture.
651	3	R. U. L. R. M. L. R. L. L.	22.4	104.2°	0
824	3	R. L. L. R. M. L.	18.1	104.2°	0
828	3	R. L. L. R. M. L.	16.2	104.6°	0
926	1	R. L. L. R. M. L.	21.2	105.6°	+
966	1	R. L. L. R. M. L.	23.0	104.8°	0
968	1	R. L. L. R. M. L. R. U. L.	22.0	104.2°	0
1023	1	R. U. L. R. M. L. R. L. L.	31.0	105.4°	+*
1024	1	R. U. L. R. M. L. R. L. L.	32.0	105.4°	+
1049	1	L. U. L. L. M. L. L. L. L.	34.0	104.8°	+
1050	1	L. U. L. L. M. L. L. L. L.	32.0	103.2°	0
6	1	L. M. L. L. L. L.	22.0	103.8°	0
822	1	R. L. L. R. M. L.	29.0	103.4°	0
43	1	R. L. L. R. M. L.	34.0	105.4°	+
45	1	R. L. L. R. M. L.	29.0	104.2°	0
60	1	L. L. L. L. M. L.	30.8	105.2°	+

* Overwhelming blood invasion.

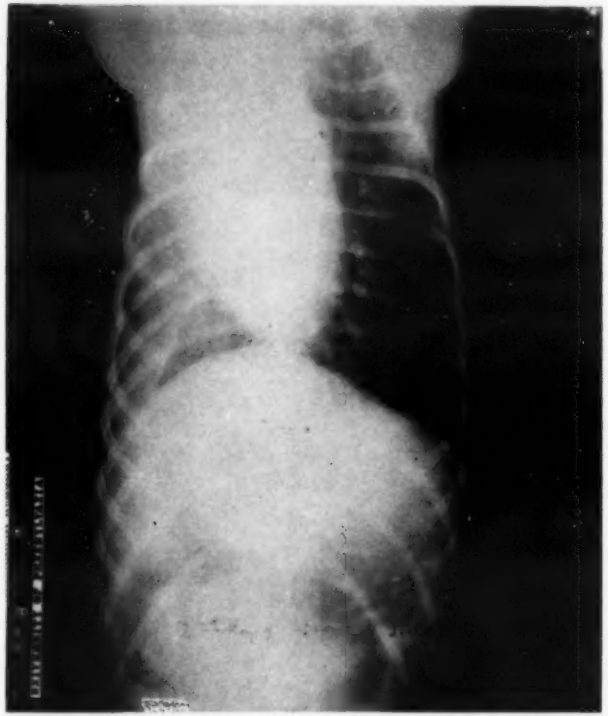


FIG. 2.—Dog No. 968. Second day of disease. Lobar pneumonia of all lobes on right side. Left lung normal.

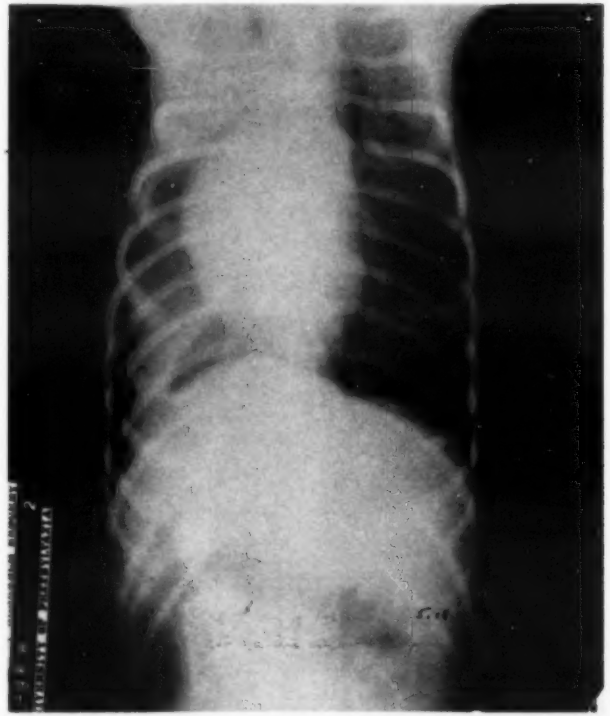


FIG. 3.—Dog No. 968. Second day of disease; after artificial pneumothorax 250 c. c. on right side. Slight compression of right lung. Left lung normal.

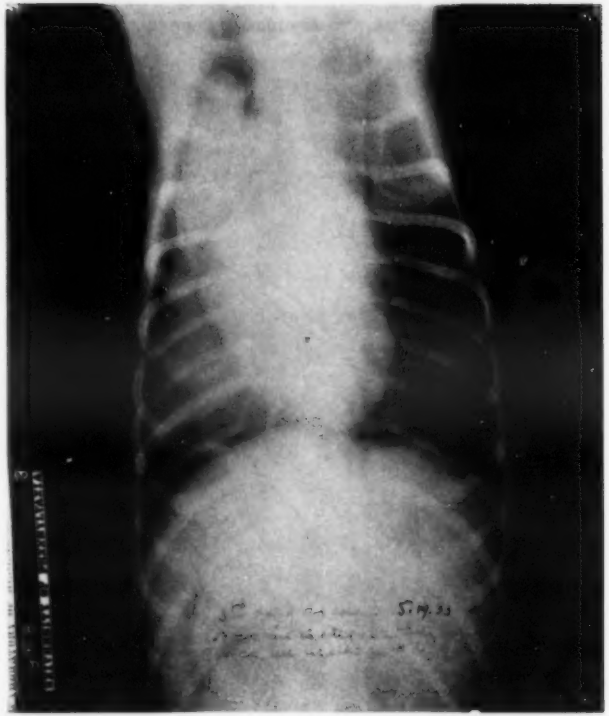


FIG. 4.—Dog No. 968. Third day of disease. After 250 c. c. of air injected on right side on second day of disease and 300 c. c. on third day. Increase in compression of right lung. Left lung normal.

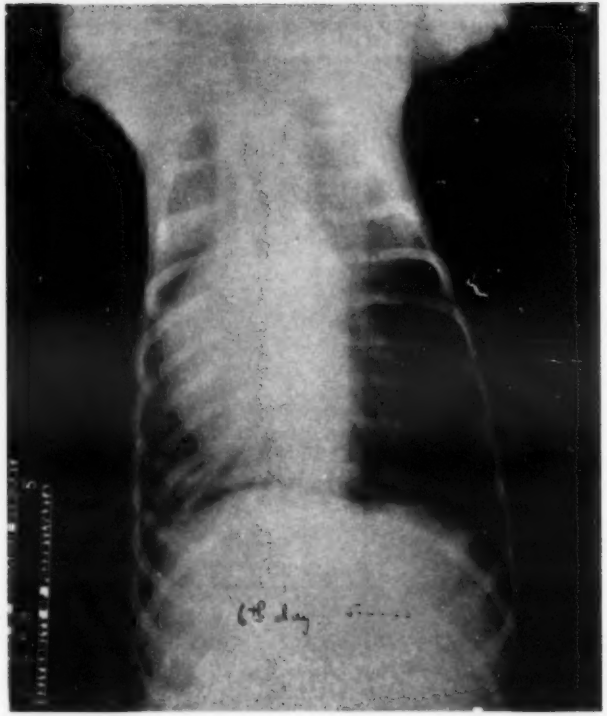


FIG. 5.—Dog No. 968. Sixth day of disease. Most of pneumothorax absorbed; beginning resolution of the right lung. Left lung normal.

FIG. 4.—Dog No. 968. Third day of disease. After 250 c. c. of air injected on right side on second day of disease and 300 c. c. on third day. Increase in compression of right lung. Left lung normal.

FIG. 5.—Dog No. 968. Sixth day of disease. Most of pneumothorax absorbed; beginning resolution of the right lung. Left lung normal.

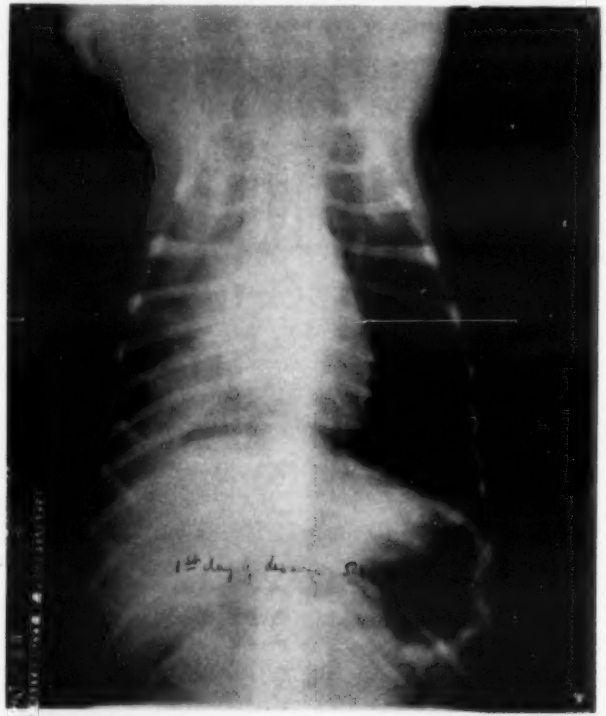


FIG. 7.—Dog No. 1024. Lobar pneumonia involving multiple lobes on right side. Normal aeration of left side.

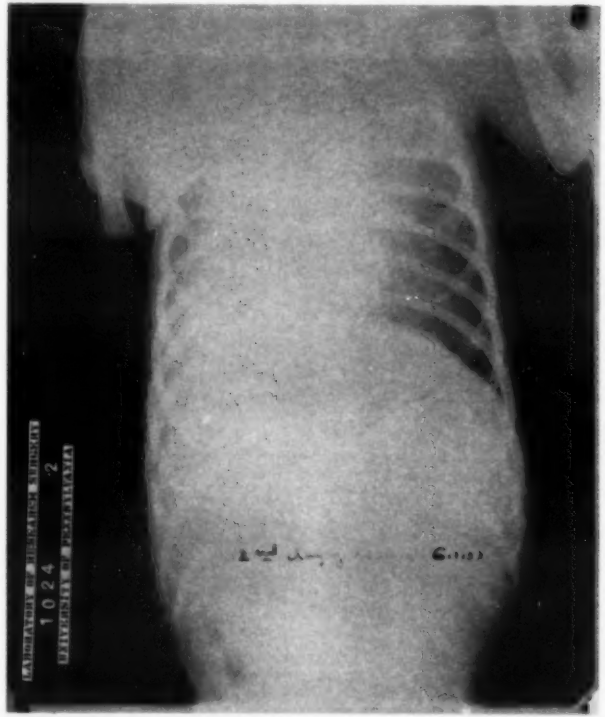


FIG. 8.—Dog No. 1024. Second day of disease. Increased density of right lung. Left side probably normal. Plate underexposed.

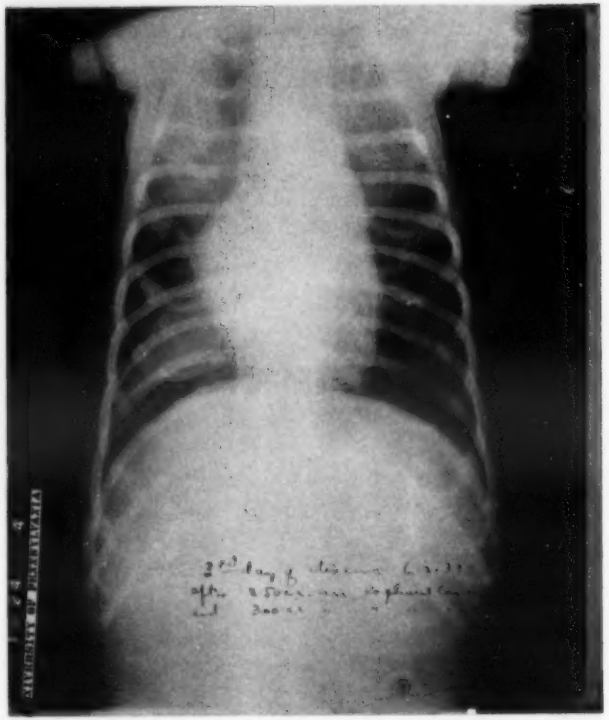


FIG. 9.—Dog No. 1024. Third day of disease, after artificial pneumothorax 250 c. c. on right side on second day and 300 c. c. on third day. Moderate compression of the lobes on right side due to pneumothorax. Left lung normal.

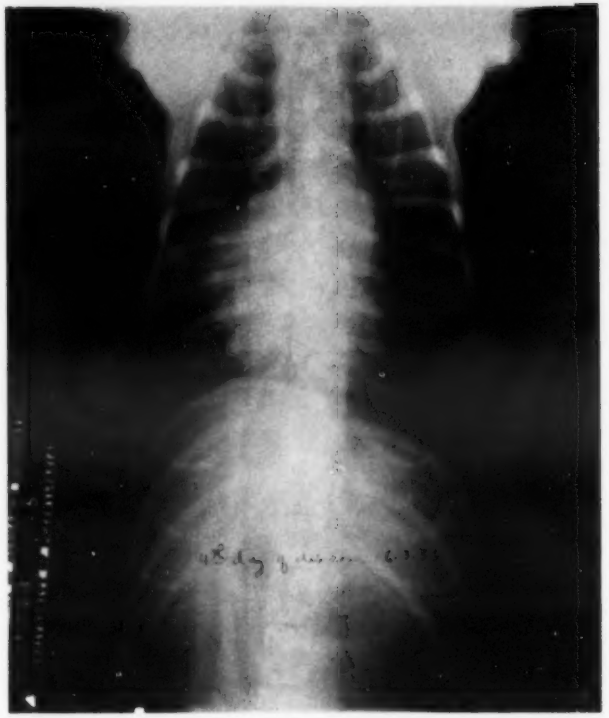


FIG. 10.—Dog No. 1024. Fourth day of disease. Appearance essentially the same as Fig. No. 9. Pneumothorax partially absorbed. Plate overexposed.

(*a*) For the sake of uniformity and convenience the day following the inoculation of the starch paste culture is called the 1st day of the disease. This differs from the terminology used by Robertson and his coworkers.[14] They showed that the pathologic process begins within a few hours after the inoculation of the starch-paste culture.

The protocols of 7 of the 15 dogs which were treated and recovered follow.

Dog 968. After the usual anesthetic (May 16) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was definitely sick and coughed a good deal. There were physical signs of extensive pulmonary consolidation of all the lobes on the right side. The respirations were deep and fast and there was much drooling from the mouth. On the following day, May 18, the dog was too sick to walk and appeared to be moribund. Artificial pneumothorax (250 cc.) was given on the right side. The following day the dog was running around the room and appeared to be well. A refill of 300 cc. of air was given. The dog made an uneventful recovery. Blood cultures were negative.

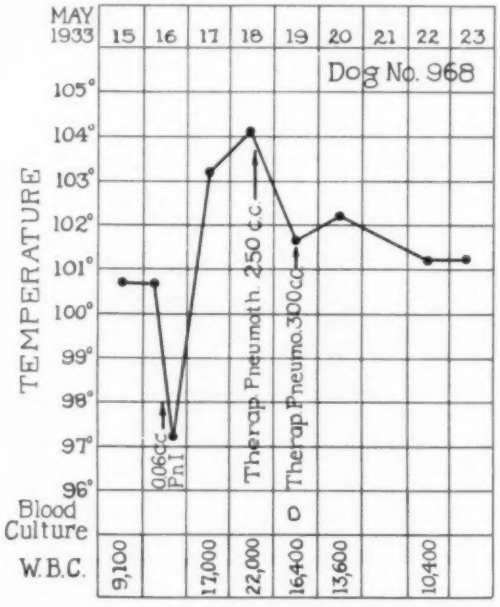


FIG. 1.—Clinical record. Dog No. 968.

Dog 1024. After the usual anesthetic (May 30) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was quite sick. The temperature was 105.2° F. and the physical signs were those of consolidation throughout the right chest. On the following day the dog was still very sick. The temperature and physical findings were unchanged. The blood culture on this day was positive. Artificial pneumothorax (250 cc.) was given on the right side. On the following day (June 2) the dog was much

better, breathing more easily and running around the room. The temperature and leukocyte count were lower. A refill of 300 cc. air was given. The dog made an uneventful recovery and appeared to be perfectly well on the following day.

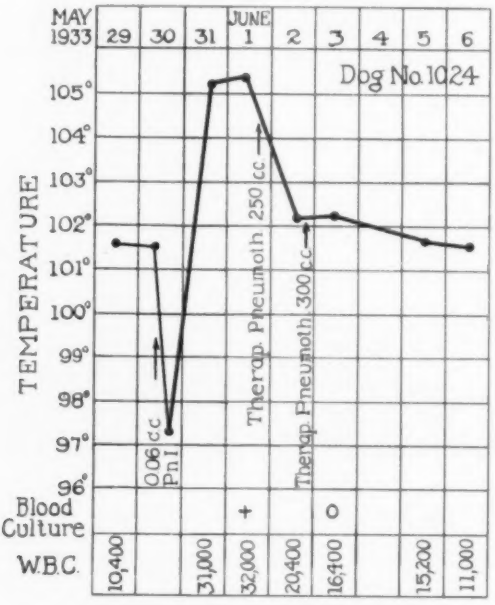


FIG. 6.—Clinical record. Dog No. 1024.

Dog 1023. After the usual anesthetic (May 30) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was definitely ill. The temperature was 104.8° F. On June 1 the dog was very sick, breathing rapidly and deeply. The temperature was 105.2° F. Blood culture taken on this day showed tremendous blood invasion (Fig. 11). Artificial pneumothorax (250 cc.) was given on the right side. On the following day the dog was still quite sick although the temperature and leukocyte count were lower. The blood culture on this day showed 5 colonies to 2 cc. of blood. A refill of 300 cc. of air was given. On June 3, the dog was better although the temperature was somewhat higher than at the time of the second treatment. From this point on, the temperature subsided and the dog made an uneventful recovery. The rise in temperature following the second treatment may have been due to the persistence of blood-stream invasion.

The interesting feature of this case was the fact that recovery followed pneumothorax treatment despite tremendous blood-stream invasion. On the day following treatment, the dog appeared to be much better and ran around the room. The temperature was, however, still elevated. This can, no doubt, be explained by the fact that the animal still had a positive blood culture of 5 colonies to 2 cc. of blood.

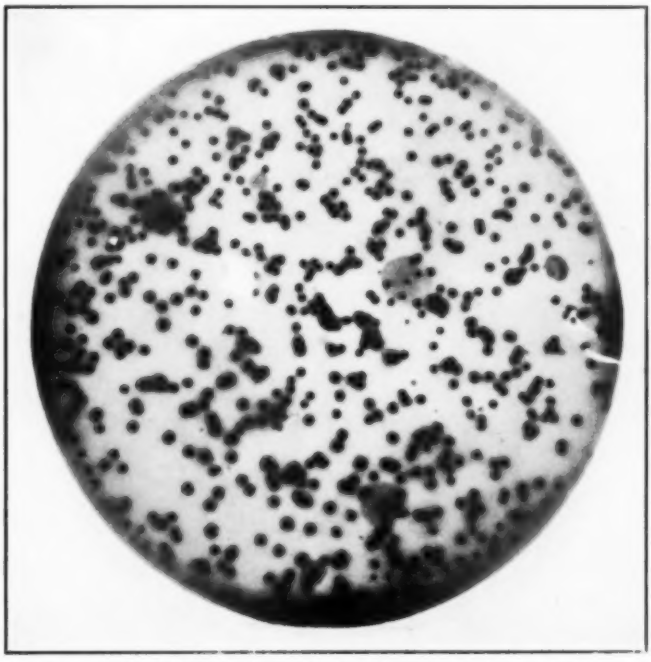


FIG. 11.—Dog 1023. Colonies from blood culture (2 cc.) on 2d day of disease (before artificial pneumothorax).

Dog 60. After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the dog was very sick and drooled at the mouth. There were physical signs of extensive consolidation on the left side. The blood culture was positive. On August 24 the animal appeared moribund. Artificial pneumothorax (300 cc.) was given on the left side. On the following day the dog was much better. The temperature was normal and the blood culture negative. On that day a refill of 250 cc. of air was given and the dog made an uneventful recovery.

Dog 1049. After the usual anesthetic (June 20) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the dog was very sick; respirations were rapid and deep, temperature was 105° F. Blood culture taken on this day was positive. On June 22 the dog appeared moribund. Artificial

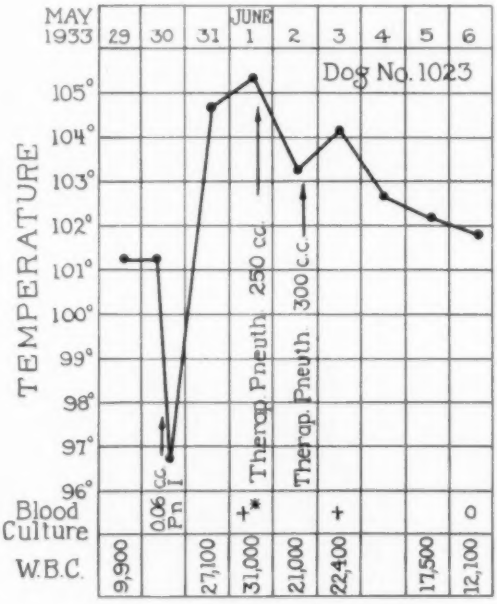


FIG. 12.—Clinical record. Dog No. 1023.

pneumothorax (250 cc.) was given on the left side. The following day the dog was much better and a refill of 300 cc. of air was given. The blood culture taken this day showed no growth. The dog made an uneventful recovery.

Dog 43. After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the dog was very sick. Respirations were rapid and deep; temperature was 105.2° F. The blood culture taken on this day was positive. On August 24 the animal was worse, panting rapidly and drooling from the mouth. Artificial pneumothorax (300 cc.) was given in the right side. On the following day the animal was much better and ran around the room. The blood culture taken on this day was negative. A refill of 250 cc. of air was given and the dog made an uneventful recovery.

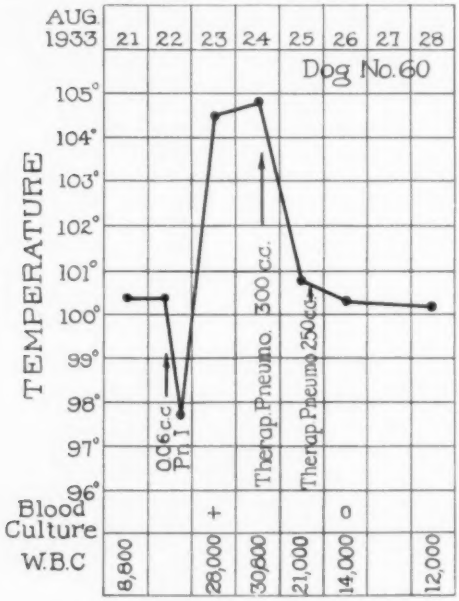


FIG. 17.—Clinical record. Dog. No. 60.

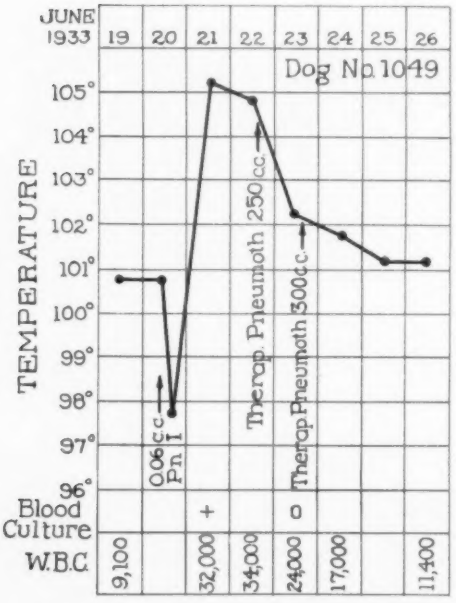


FIG. 22.—Clinical record. Dog No. 1049.

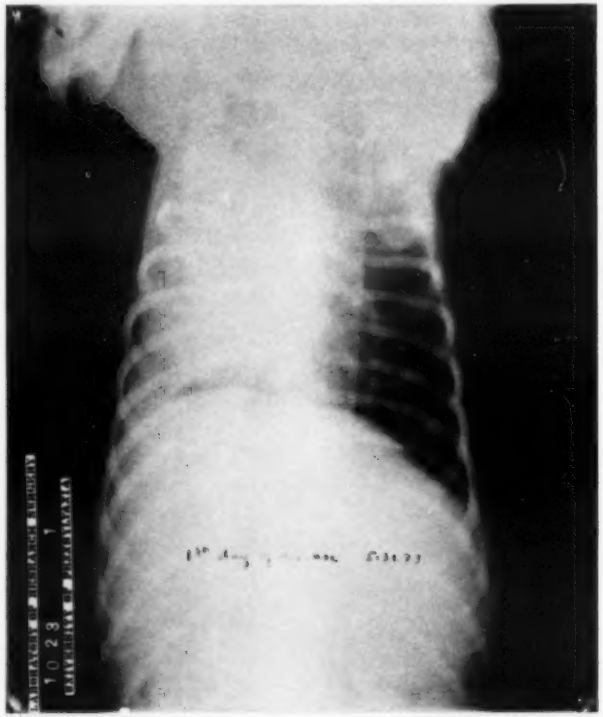


FIG. 13.—Dog No. 1023. Lobar pneumonia involving all lobes on right side. Left lung aerating normally. Heart displaced to affected side.

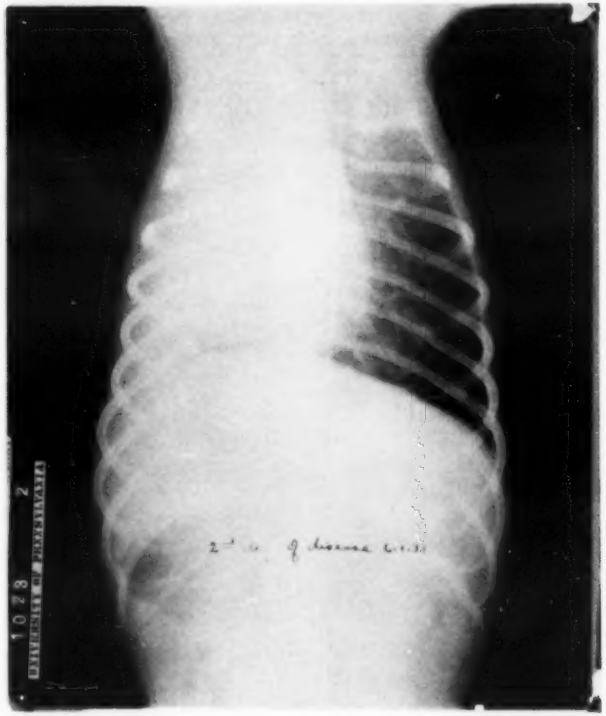


FIG. 14.—Dog No. 1023. Involvement of right lung by lobar pneumonia is shown to better advantage. Heart displaced to affected side. Left lung aerating normally.

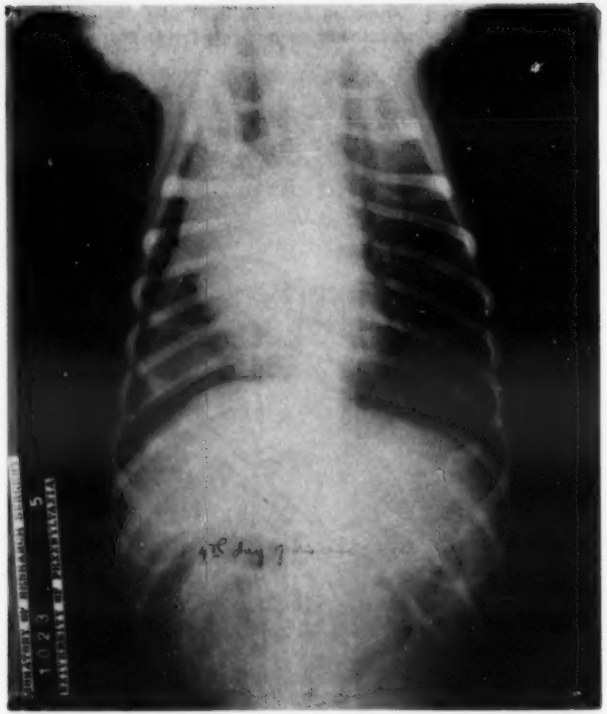


FIG. 15.—Dog No. 1023. Fourth day of disease after artificial pneumothorax 250 c. c. on second day and 300 c. c. on third day of disease. Moderate compression of lobes on right side. Normal aeration of left side.

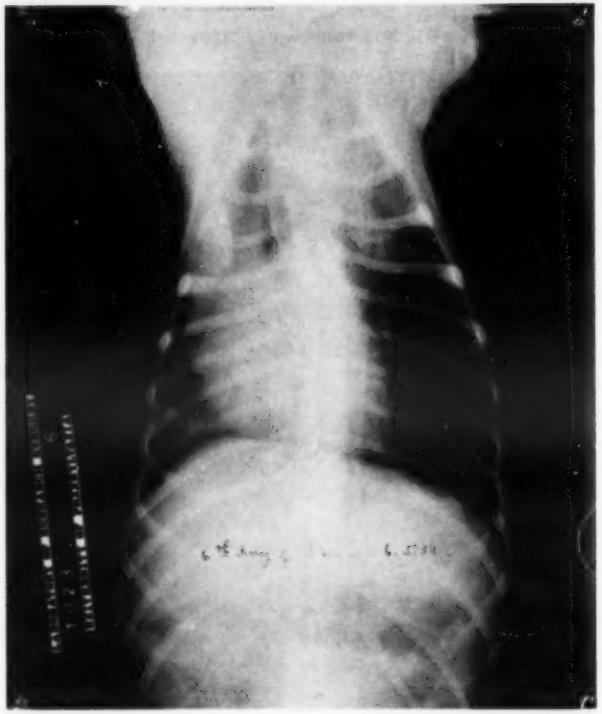


FIG. 16.—Dog No. 1023. Sixth day of disease. The pneumothorax is largely absorbed. Considerable resolution has taken place.

of disease. Moderate compression of lobes on right side. Normal aeration of left side.

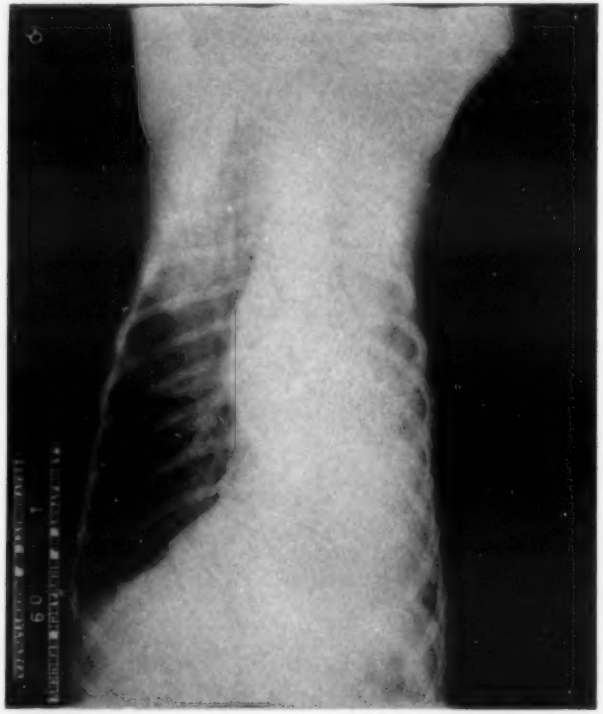


FIG. 18.—Dog No. 60. First day of disease. Increased density of all lobes on left side. Right lung aerating normally.

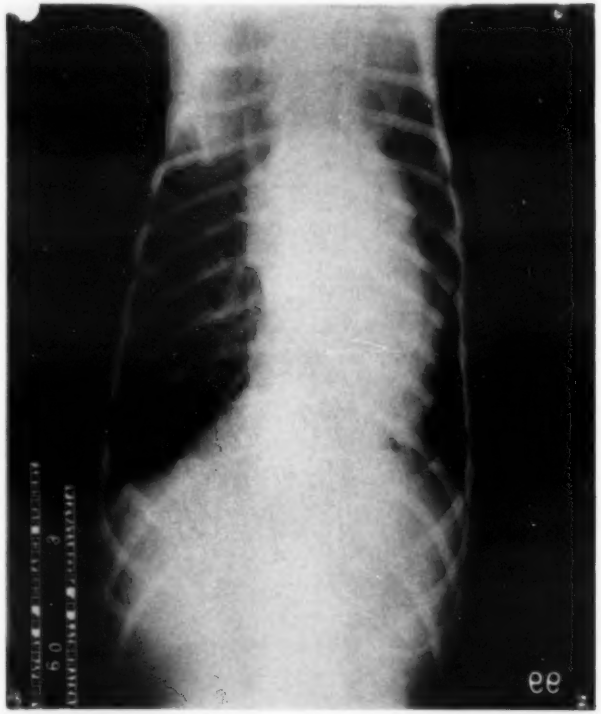


FIG. 19.—Dog No. 60. Second day of disease; after artificial pneumothorax 250 c. c. left side. Moderate compression of left lung due to pneumothorax.

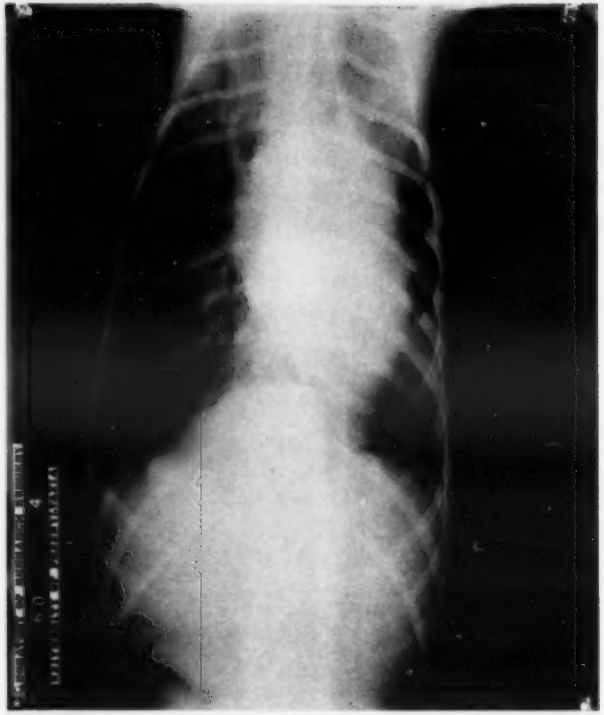


FIG. 20.—Dog No. 60. Third day of disease after artificial pneumothorax 250 c. c. on second day of disease and 300 c. c. on third day. Considerable compression of left lung due to artificial pneumothorax. Right lung aerating normally.

FIG. 21.—Dog No. 60. Fourth day of disease. Beginning re-expansion of left lung with beginning resolution. Right lung aerating normally.

day. Considerable compression of left lung due to artificial pneumothorax. Right lung aerating normally.

aerating normally.

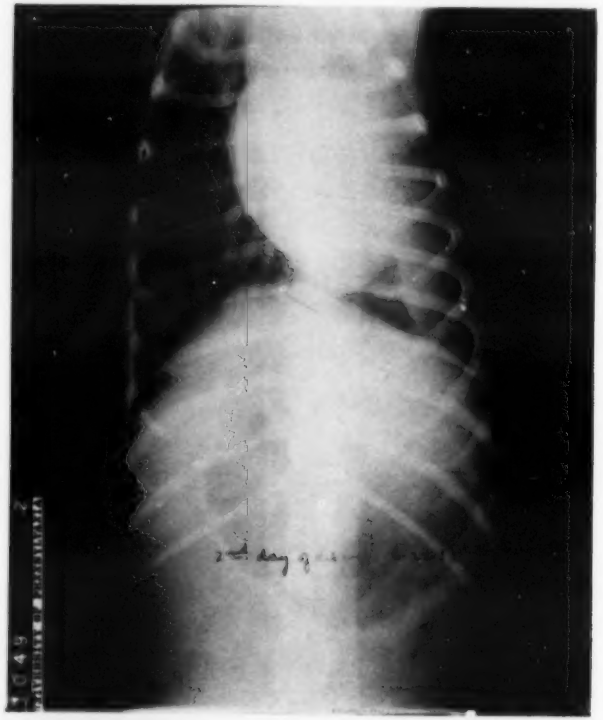


FIG. 23.—Dog No. 1049. Second day of disease. Lobar pneumonia involving two of the lobes and possibly the third on left side. Right lung aerating normally.

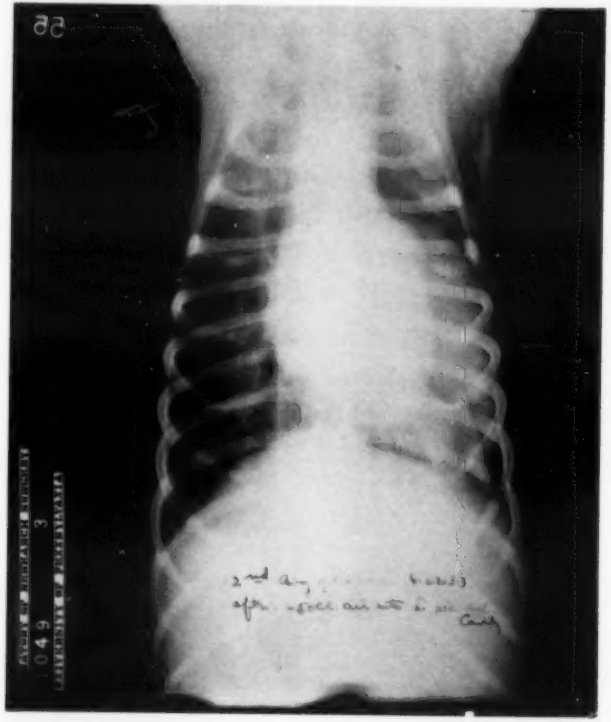


FIG. 24.—Dog No. 1049. Second day of disease after artificial pneumothorax 250 c. c. (left). Moderate compression of lobes on left due to pneumothorax. Right lung aerating normally.

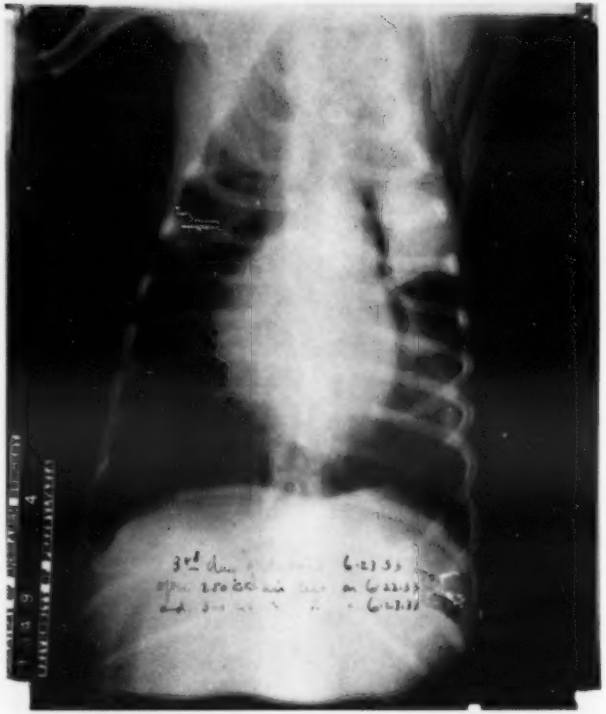


FIG. 25.—Dog No. 1049. Third day of disease after 250 c. c. air on second day of disease and 300 c. c. on third day. Moderate compression left lung with beginning clearing of left lower lobe.

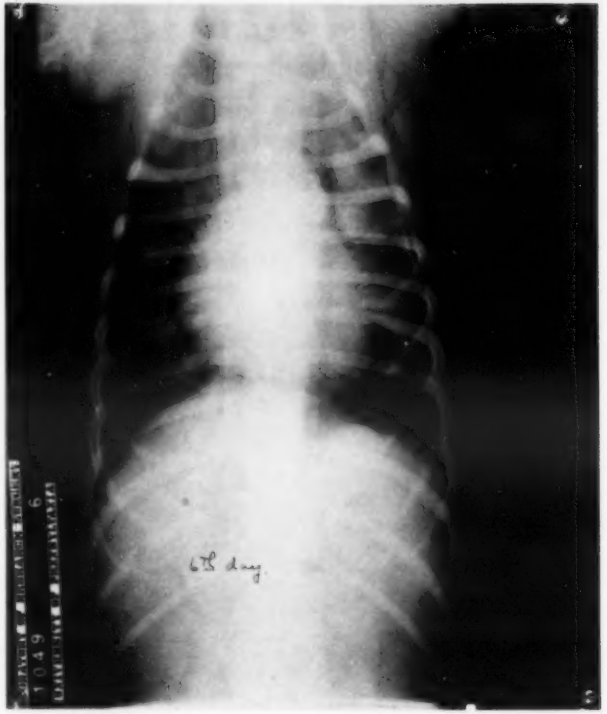


FIG. 26.—Dog No. 1049. Sixth day of disease. The pneumothorax has largely disappeared and there has been a considerable amount of resolution. Right lung normal.

compression left lung with beginning clearing of left lower lobe.

of resolution. Right lung normal.

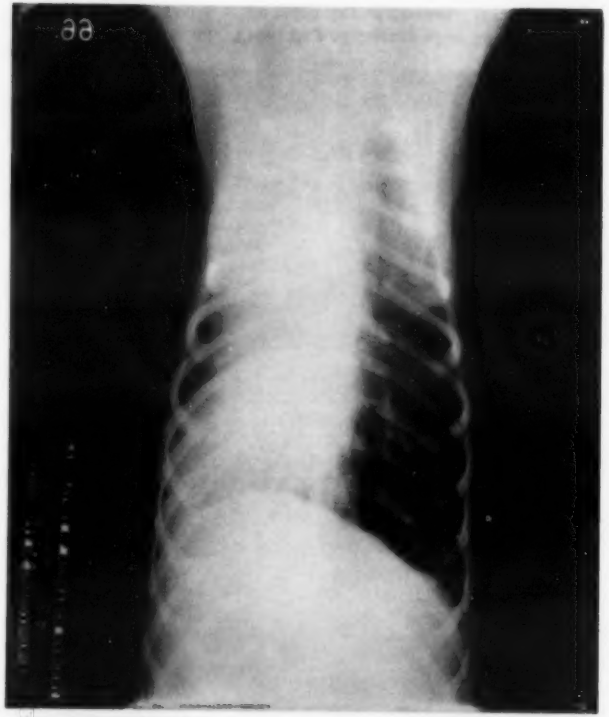


FIG. 28.—Dog No. 43. First day of disease; lobar pneumonia involving the upper and lower lobes and partial involvement of mid-lobe on right side. Left lung normal.

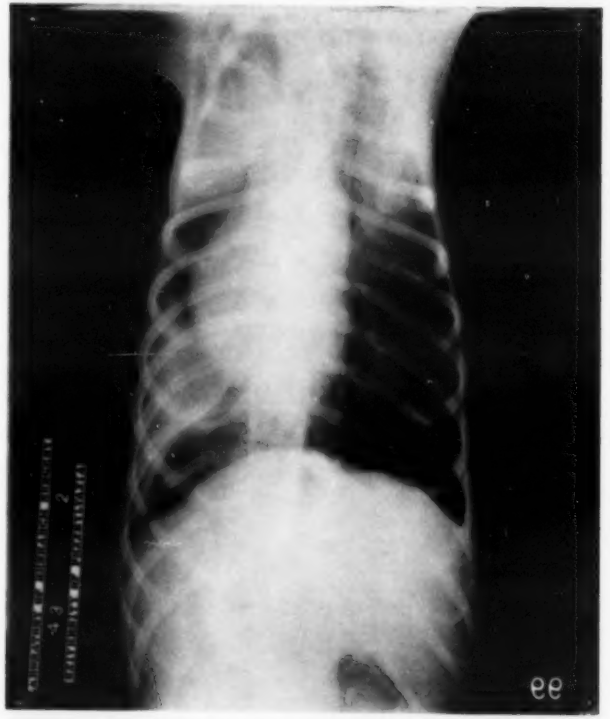


FIG. 29—Dog No. 43. Second day of disease, after artificial pneumothorax 250 c. c. on right side. Moderate compression of right lung.

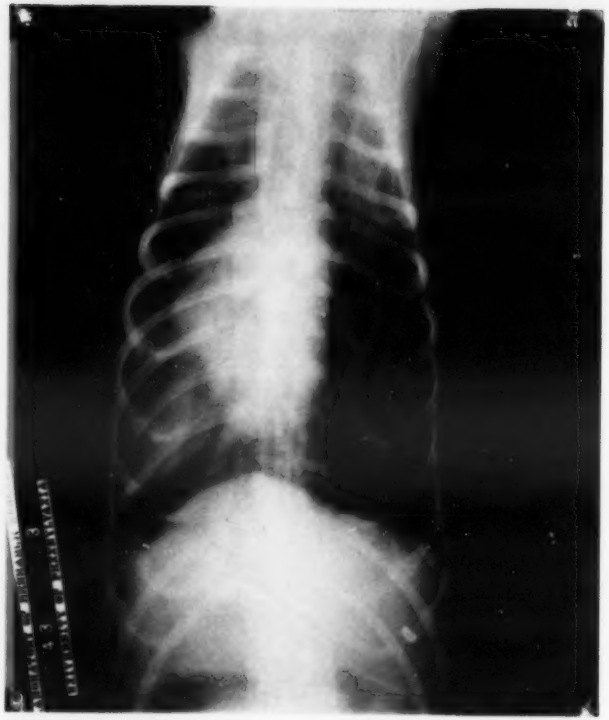


FIG. 30.—Dog No. 43. Third day of disease after 250 c. c. air on second day and 300 c. c. on third day of disease. Increased compression right side. Heart toward affected side.

FIG. 31.—Dog No. 43. Fifth day of disease. Considerable absorption of the pneumothorax. Right lung shows resolving pneumonia. Heart still toward affected side. Left lung normal.

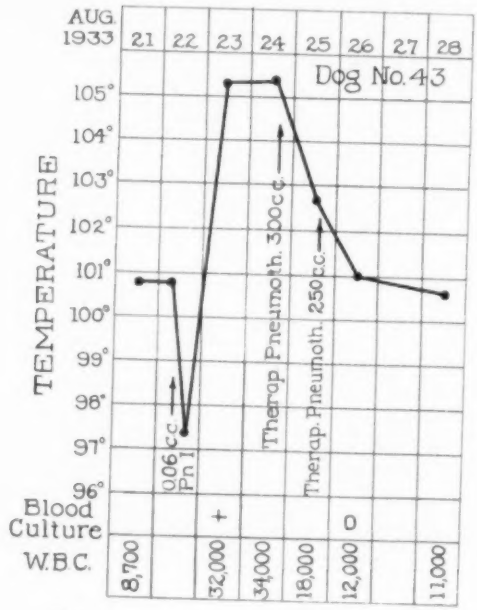


FIG. 27.—Clinical record. Dog No. 43.

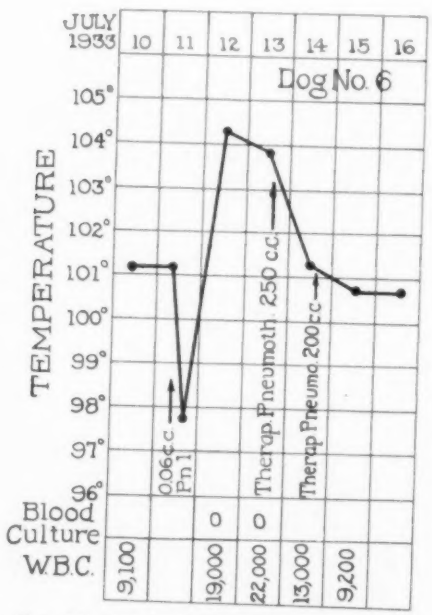


FIG. 32.—Clinical record. Dog No. 6.

Dog 6. After the usual anesthetic (July 11) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the left lower lobe. On the following day the animal was definitely sick. The temperature was 104.2° F. The blood culture taken on this day showed no growth. On July 13 the dog appeared more acutely ill and breathed rapidly and deeply. Artificial pneumothorax of 250 cc. was given on the left side. On the following day the dog was much better, ate well and ran around the room. A refill of 200 cc. of air was given on this day. The dog made an uneventful recovery.

In our series of 36 dogs, 18 were treated with artificial pneumothorax on the 2d day of the disease with 15 recoveries and 3 deaths. The 2d day was chosen as the disease produced in this way was thought to have reached its height at about that time.

On the day following the initial injection of air there was, with two exceptions (Dogs 650 and 925) marked improvement in the condition of the animals. A further refill was given on the day following the initial injection. No subsequent injections were given and no other form of therapy was used at any time.

The pulmonary compression resulting from the introduction of 250 or 300 cc. of air produced in the animals a condition analogous to the crisis seen in lobar pneumonia in man. There was an abrupt drop of temperature and leukocyte count, with easier and more normal respirations and an appearance of wellbeing. The dogs promptly recovered sufficiently to walk and take food. The blood cultures in those dogs in which there was blood invasion before the institution of artificial pneumothorax were usually negative on the day after the treatment, and in the 1 case (Dog 1023) where the blood stream invasion was extraordinarily severe it was found to be reduced to 5 colonies per 2 cc. of blood on the day after the second treatment.

An analysis of the 3 deaths which occurred in those animals which were treated with artificial pneumothorax follows:

TABLE 3.—DATA OF DOGS DYING AFTER TREATMENT.

Dog No.	Type pneu.	Involv.	W.B.C. in thousands.	Temp.	Blood culture.	Remarks.
650	3	R. L. L. R. M. L.	23.4	104.2°	0	150 cc. air 2d day. 150 cc. air 3d day. Died 6th day.
925	1	R. U. L. R. M. L. R. L. L.	26.0	104.8°	0	Died 5th day. Lung abscess and sanguinoserous pleurisy.
61	1	R. L. L. R. M. L.	30.0	105.2°	0	Died 5th day. Hemor. enteritis.

Dog 650. After the usual anesthetic (March 15), 0.06 cc. sedimented pneumococci Type 1 in 1 cc. of starch paste was injected into the right lower lobe. On the following day the temperature was elevated to 104.6° F. and

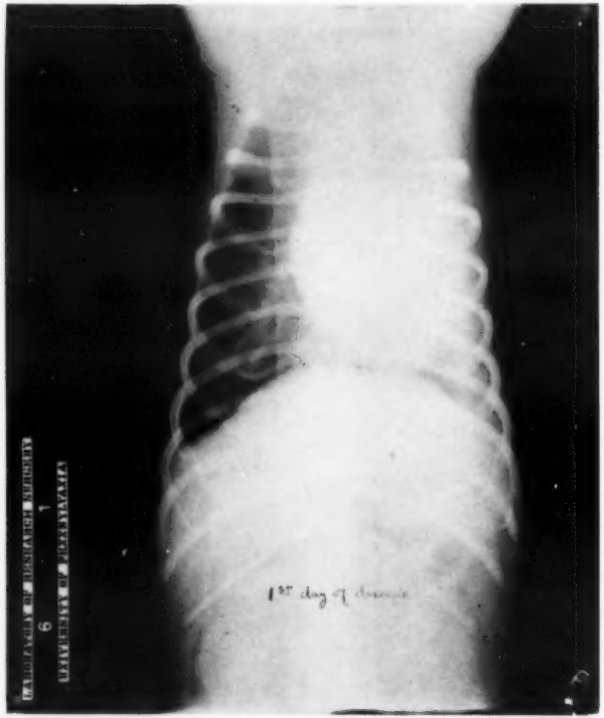


FIG. 33.—Dog No. 6. First day of disease; lobar pneumonia involving the lobes on left side. Heart toward the affected side. Normal aeration of right side.

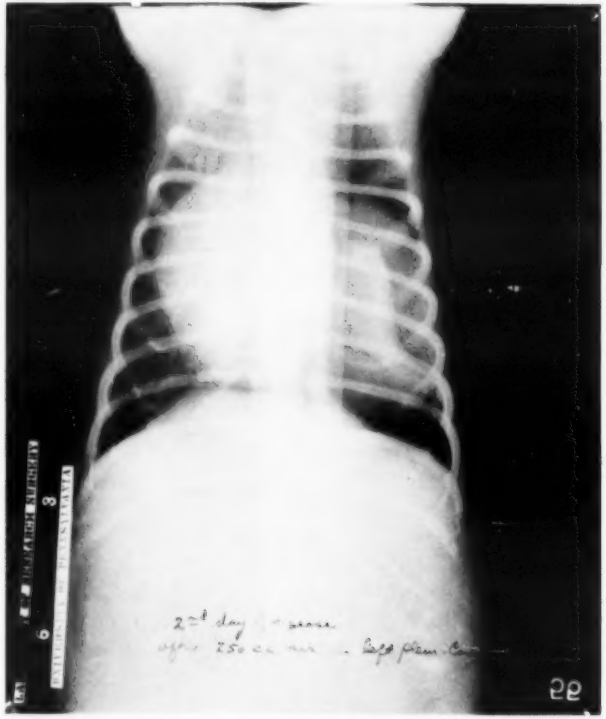


FIG. 34.—Dog No. 6. Second day of disease, after artificial pneumothorax 250 c. c. Considerable compression of lobes on left. Heart displaced away from affected side. Normal aeration of right lung.

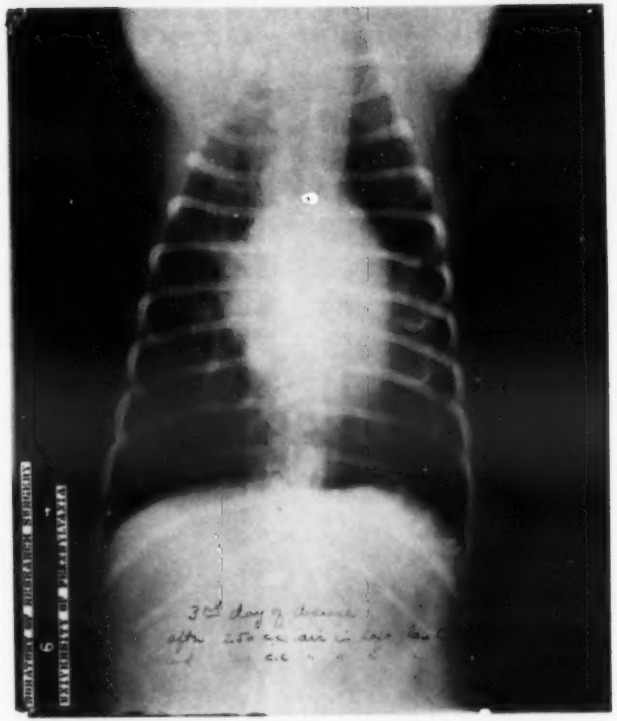


FIG. 35.—Dog No. 6. Third day of disease, after 250 c. c. air on second day of disease and 300 c. c. on third day. Considerable compression of lobes on left. Heart in mid-line. Normal aeration of right lung.

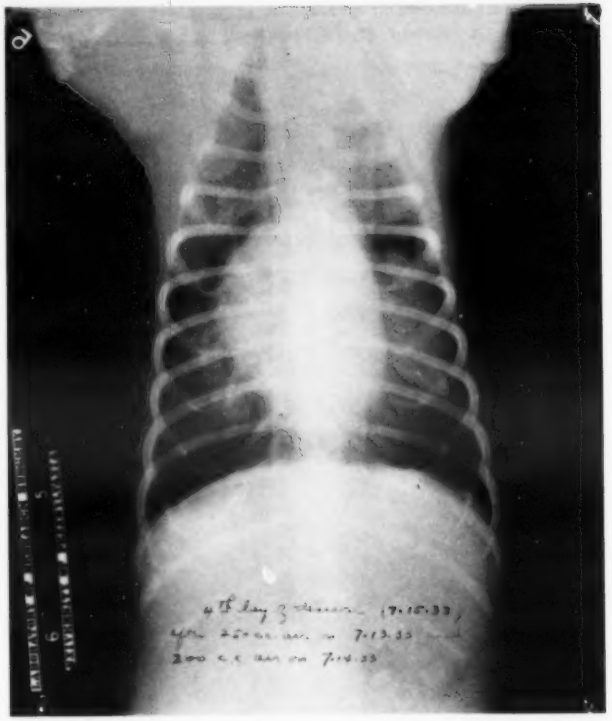


FIG. 36.—Dog No. 6. Moderate amount of pneumothorax still present. Density of diseased lung not as great as on previous examination suggesting that there is beginning resolution. Heart slightly to the right.

second day of disease and 300 c. c. on third day. Considerable compression of lobes on left. Heart in mid-line. Normal aeration of right lung.

present. Density of diseased lung not as great as on previous examination suggesting that there is beginning resolution. Heart slightly to the right.

FIG. 37.—Dog No. 925. Second day of disease. Beginning consolidation of all lobes on right side. Heart in normal position.

FIG. 38.—Dog No. 925. Second day of disease after injection of 275 c. c. of air on right side. Moderate pneumothorax present.

FIG. 39.—Dog No. 925. Third day of disease after 275 c. c. of air on second day and 250 c. c. of air on third day. Consolidation of all lobes on the right side and moderate pneumothorax. Small circular cavity (abscess) in right lower lobe.

of all lobes on the right side and moderate pneumothorax. Small circular cavity (abscess) in right lower lobe.

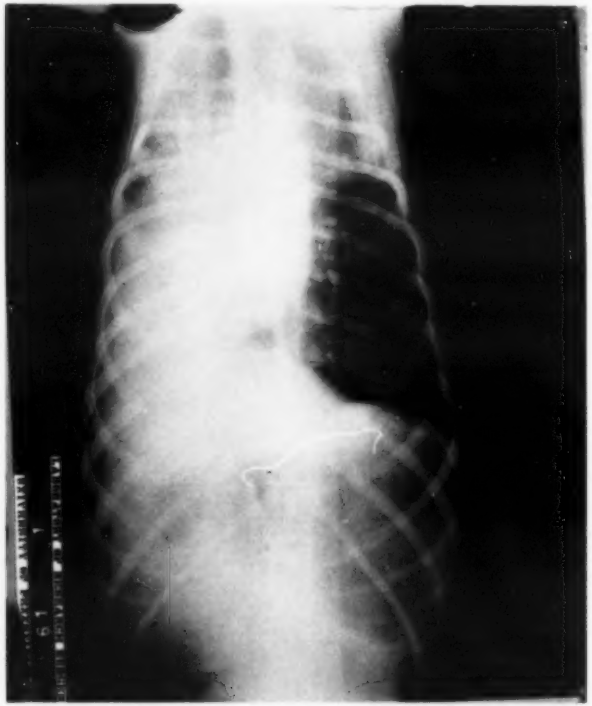


FIG. 40.—Dog No. 61. First day of disease. Complete consolidation of all lobes on right side. Heart toward affected side.

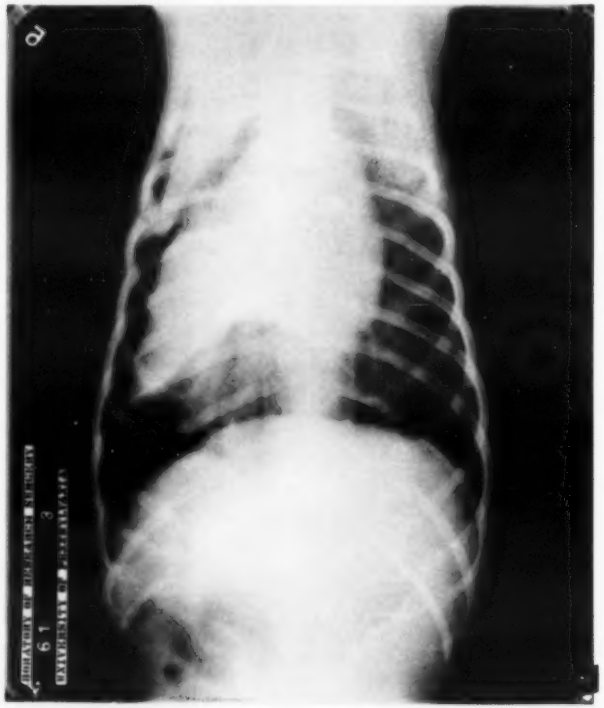


FIG. 41.—Dog No. 61. Third day of disease after 300 c. c. air on right side on second day and 250 c. c. on third day. Compression of all lobes on right side by pneumothorax. Heart in normal position.

FIG. 42.—Dog No. 61. Fourth day of disease. Resolving pneumonia of all lobes on the right side. Some pneumothorax still present. Heart in normal position.

present. Heart in normal position.

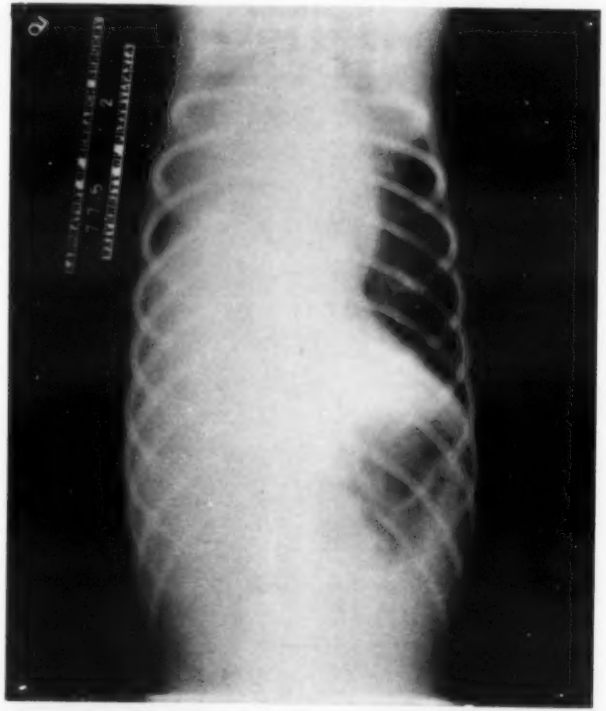


FIG. 43.—Dog No. 775. Fourth day of disease. Consolidation of all lobes on right side.

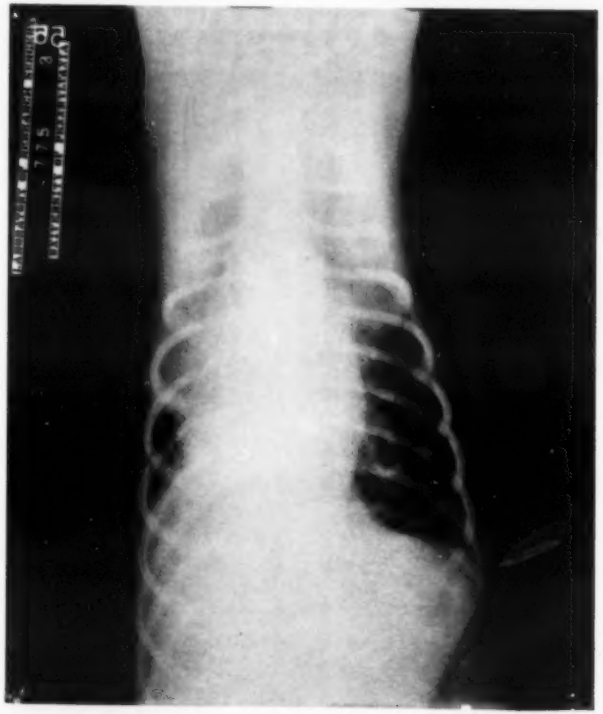


FIG. 44.—Dog No. 775. Fifth day of disease. Dense consolidation of upper and lower lobes. Slight clearing of mid zone. Death occurred on the eleventh day.

FIG. 45.—Dog No. 827. First day of disease. No evidence of consolidation.

FIG. 46.—Dog No. 827. Second day. Complete consolidation of right upper lobe and right middle lobe. Heart drawn slightly to affected side. Death occurred on third day.

the leukocyte count was 24,000. The blood culture was negative. On March 17 the dog looked very sick. The temperature was 104.2° F. Artificial pneumothorax (150 cc.) was given on the right side. On the following day the animal appeared improved. The temperature was 103.4° F. and the leukocyte count 21,000. A refill of 150 cc. of air was given. On March 19 the dog was more active and breathed easier. The leukocytes numbered 11,400 and temperature was 104.2° F. Two days later the dog appeared to be worse and died the following day.

Postmortem examination revealed gray hepatization of the right middle and lower lobes. There was no fluid in the pleural cavities. The left lung appeared normal. This dog died of uncomplicated pneumonia. The temperature was not materially influenced by either the first or second treatment. The amount of air introduced at each of our instillations, in the light of our subsequent experience, may have been insufficient to produce the characteristic response.

Dog 925. After the usual anesthetic (May 9) 1 cc. of starch paste, containing 0.06 cc. of sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was very sick; the temperature was 104.8° F. and the leukocyte count 16,000. Artificial pneumothorax (275 cc.) was given on the right side. On May 13 the dog appeared to be just as sick as before the treatment was given. The temperature was 104.2° F., leukocyte count 22,000. The dog coughed a good deal and expectorated a thick mucoid material. A refill of 250 cc. of air was given. The animal became steadily worse and died on May 15.

Postmortem examination revealed both pleural cavities filled with bloody fluid. Cultures made from this showed a mixed growth of organisms with pneumococci predominating. The entire right lung was in a state of gray hepatization. The left lung, except that it was water-logged (soaked in the pleural fluid) looked normal. In the right lower lobe there was a dark indentation of the lung with surrounding softening of the lung tissue. This proved to be an abscess and its location corresponded with the interspace where the initial needle puncture was made in giving the artificial pneumothorax.

This dog did not react as did the others to the artificial pneumothorax. We think it is fair to surmise that at the time of the initial injection of air the needle, as the result of improper technique, penetrated the lung with resulting abscess and empyema.

Dog 61. After the usual anesthetic (August 22) 1 cc. of starch paste, containing 0.06 cc. sedimented pneumococci Type 1, was injected into the right lower lobe. On the following day the animal was very sick; temperature 105.4° F., leukocyte count 31,000. On August 24 the dog was still sicker. Artificial pneumothorax (300 cc.) was given on the right side. The following day the animal was much better; the temperature was 102.4° F., leukocytes 22,000. A refill of 250 cc. of air was given. At this time the dog had some abdominal distention and a bloody diarrhea. A roentgenogram showed good compression on the right side. The bloody diarrhea and abdominal distention persisted and the dog died on the following day.

In view of the satisfactory response to treatment, confirmed roentgenographically (Figs. 40, 41 and 42), we believe, in view of the hemorrhagic enteritis, that this dog died of an unrelated intercurrent infection. We regret the fact that this animal was the only one in the entire series which was not examined postmortem.

Of the 18 untreated dogs used as controls, 13 died and 5 recovered.

At postmortem each of the 13 animals showed unilateral consolidation. These dogs died, for the most part, on the 2d or 3d day of the disease. At the time of death the lesion had always extended to more than one lobe and usually involved the entire lung, which was in the stage of grayish-red hepatization. A variable amount of fibrinous pleurisy was present over the consolidated lung. The pleuræ contained no fluid.

TABLE 4.—DATA OF UNTREATED DOGS THAT DIED.

Dog No.	Type pneu.	Involv.	W.B.C. in thousands	Temp.	Blood culture	Remarks.
775	3	R. U. L. R. M. L. R. L. L.	26.0	102.8°	0	Died 11th day.
827	3	R. U. L. R. M. L.	14.4	103.8°	0	Died 3d day.
927	1	R. M. L. R. L. L.	17.8	103.2°	+	Died 2d day.
928	1	R. L. L. R. M. L.	18.1	101.8°	+	Died 2d day.
965	1	R. U. L. R. M. L. R. L. L.	18.8	104.2°	+	Died 2d day.
967	1	R. L. L. Part of R. M. L.	23.0	104.2°	0	Died 3d day.
1021	1	R. U. L. R. M. L. R. L. L.	27.0	104.2°	+	Died approx. 60 hr. after inoculation.
1022	1	R. U. L. R. M. L. R. L. L.	30.0	104.8°	..	Died approx. 36 hr. after inoculation. Heart blood +.
1046	1	L. U. L. L. M. L. L. L. L.	25.0	104.2°	+	Died approx. 36 hr. after inoculation.
1047	1	L. U. L. L. M. L. L. L. L.	26.4	104.4°	+	Died 3d day.
8	1	L. U. L. L. M. L. L. L. L.	22.0	103.4°	+	Died 3d day.
46	1	R. L. L. R. M. L.	31.0	102.4°	0	Died approx. 60 hr. after inoculation.
59	1	L. L. L. L. M. L.	....	.....	..	Died approx. 24 hr. after inoculation. Heart blood +.

Of the 5 dogs which recovered without treatment only 1 had a positive blood culture. These dogs recovered by crisis on the 4th or 5th day of the disease.

Changes of Position of Thoracic Viscera During Experimental Pneumonia. Some of our dogs, by roentgenogram, before introduction of air, showed cardiac and mediastinal displacement toward the affected side and elevation of the diaphragm on the same side. This was observed also by Robertson and his coworkers.[14] They

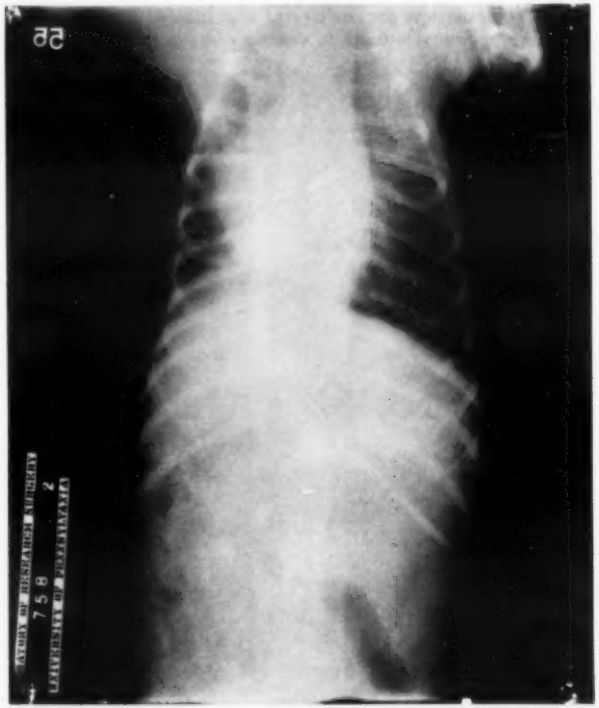


FIG. 47.—Dog No. 758. Second day of disease. Beginning consolidation of all lobes on right side. Heart toward affected side.

FIG. 48.—Dog No. 758. Third day of disease. Spontaneous resolution of all lobes on right side. Heart in normal position. Uneventful recovery.

FIG. 49.—Dog No. 62. First day of disease. Consolidation of all lobes on right side. Heart toward affected side.

FIG. 50.—Dog No. 62. Third day of disease. Beginning spontaneous resolution in right lower lobe. Heart still toward affected side. Positive blood culture. Uneventful recovery.

found that when the disease process spread rapidly, such as that which occurred after large doses of the pneumococci were injected, the heart shadow showed an early and marked displacement toward the affected side. Even with densely consolidated lung this displacement was observed. Wu,[18] in a study of visceral displacement

TABLE 5.—DATA OF UNTREATED DOGS THAT RECOVERED.

Dog No.	Type pneu.	Involv.	W.B.C. in thousands.	Temp.	Blood culture.
758	3	R. U. L. R. M. L. R. L. L.	23.0	102.6°	0
830	3	L. U. L. L. M. L. L. L. L.	15.4	104.6°	0
1055	1	R. L. L.	26.0	102.8°	0
44	1	R. L. L. R. M. L.	28.4	104.2°	0
62	1	R. L. L. R. M. L.	29.0	104.0°	+

in pneumonia, found in 40 consecutive cases of lobar pneumonia in human subjects that 5 showed displacement of the heart and trachea to the affected side and 22 elevation of the diaphragm on that side. In 105 cases of experimental pneumonia in dogs (Robertson's study[14]) there were 42 instances of visceral displacement toward the affected side.

Summary and Conclusions. Since 1921, several foreign clinicians have used therapeutic pneumothorax on the affected side in lobar pneumonia, with 47 recoveries and 3 deaths. Despite these optimistic reports we have found no published experimental data on this subject and we therefore undertook a study on animals in an effort to define and justify, if the evidence so warranted, the use of this treatment in man.

We have therefore produced lobar pneumonia in 36 dogs (Robertson method) 18 of which were treated by artificial pneumothorax and a like number used as controls. Observations on the course of the disease included clinical study, daily leukocyte determinations, blood cultures and roentgenograms. No other treatment was employed in either group and no attempt was made to control the behavior or feeding of the animals.

Both the clinical reports in the literature and our experimental study indicate that the introduction of air in the pleural cavity in proper amount on the affected side produces, temporarily at least, a picture comparable to the crisis in lobar pneumonia and achieves an artificial limitation of an otherwise self-limited disease. In addition to this, in the experimental animal, this treatment appears to have a favorable effect on the blood-stream invasion.

We are not prepared at this time to offer any explanation for the *modus operandi* of this method of treatment. We most emphatically

do not recommend artificial pneumothorax as a routine procedure in all cases of lobar pneumonia.

We believe that the clinical and experimental data which have been presented amply justify this treatment in selected cases of unilateral pneumococcic lobar pneumonia, with due regard for the danger of circulatory collapse incident to the cardiac and mediastinal displacement which may result from its use.

We agree entirely with Coghlan that lobar pneumonia is emphatically not the disease in which to acquire experience in the technique of artificial pneumothorax.*

* We have very recently had opportunity to treat by this method 1 patient, a male, aged 44, with lobar pneumonia, who was admitted December 2, 1933, to this hospital on Dr. Stengel's service, on the 3d day of the disease. On the following day, immediately before treatment, his temperature was 102.8° F., pulse 136, respirations 36 and the physical signs were those of complete consolidation of the left lower lobe. At 3 P.M. 400 cc. of air was administered. Profuse perspiration began almost immediately with an immediate fall in temperature which reached 99° F. at 9 o'clock the following morning. At this time the respirations were 24 and the pulse, which had dropped more slowly than the temperature, was 114. The physical signs of consolidation, which had become completely masked by the first treatment, reappeared at this time, indicating that the air had been largely absorbed. For this reason, another injection of 400 cc. of air was given. During that day the temperature reached 100° F. on one occasion. It then became normal. Within 7 hr. after the initial treatment, the patient was entirely comfortable and so remained. Examination of the sputum revealed pneumococcus Type 1. The blood cultures were sterile. Daily roentgenograms were comparable in all respects to those obtained in the experimental animals, similarly treated, with the exception that 400 cc. of air in this patient, who weighed 165 pounds, caused considerable cardiac and mediastinal displacement to the unaffected side. For some reason which we do not understand, a dog of 10 kg. will tolerate and actually require a much larger instillation proportionately than man. In man, the solid lobe or lung occupies a considerable amount of space in the pleural cavity despite the fact that it is more compressible than one would imagine. This case report with others will be the subject of another publication.

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PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS.*

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The process of healing of tuberculosis is essentially the same in the lungs of patients treated with rest alone or when in addition pneumothorax is utilized. In the presence of pneumothorax recovery ensues not so much as a result of the collapse of the lung *per se*, but indirectly as a result of the better opportunity it offers a resistant individual for the fixation of the diseased parts by fibrosis and calcification. As a clinical corollary, one observes that the course of patients with relatively benign bilateral disease is more often influenced favorably in both lungs under the effects of pneumothorax treatment of the more actively diseased lung than is the course of patients with acute pneumonic phthisis that is limited to one lung. Indeed the tuberculous process may spread from a relatively limited focus and undergo caseation and cavitation in the presence of a pneumothorax. The general acceptance of partial compression with pneumothorax in the treatment of pulmonary tuberculosis, unfortunately an enforced procedure in most instances, also bespeaks a biologic rather than a mechanical factor as playing the predominant rôle in arresting the disease.

With pneumothorax, there results more or less contraction of the affected parenchyma, stasis of the blood and lymph flow and immobilization of the chest wall preventing further extension of the disease. After the pneumothorax is discontinued, the heart, mediastinum and diaphragm are almost invariably displaced to the diseased side and act as an additional tampon on the fibrotic and, not infrequently, bronchiectatic lung. This is apt to follow particularly fibro-ulcerative, pleuro-pulmonary tuberculosis that had been subjected to prolonged compression. In many favorable instances this constitutes the end result, the tuberculous process being held in check leading to clinical arrest of the disease. Under proper conditions, this mode of healing of pulmonary tuberculosis occurs also in patients who recover without the aid of collapse therapy.

In some patients, after pneumothorax has been discontinued and the lung has re-expanded, one obtains roentgenologic evidences of anatomic healing as shown by the disappearance of cavities and

* This study was aided by a grant from the Board of Trustees of Montefiore Hospital.

absorption of tuberculous infiltration. Quite often, in these instances, there is little or no displacement of intrathoracic structures although the diseased lung may have harbored cavities of considerable size. This mode of healing is characteristic of benign, exudative types of pulmonary tuberculosis situated below the level of the clavicles. In this respect also it appears that pulmonary tuberculosis which responds to pneumothorax by resolution is of a type that behaves in a similar manner without the aid of pneumothorax. In other words, pneumothorax does not heal pulmonary tuberculosis. Its therapeutic value lies primarily in its ability to put the affected lung in an ideal state for natural processes of healing to take place. This explains why some patients, particularly those with fibroulcerative tuberculosis, require pneumothorax for a considerable duration and are liable to reactivations even after 3 or 4 years of collapse therapy, while others, particularly those with so-called infraclavicular tuberculosis, often get well after a comparatively short period of treatment.

Indications for Pneumothorax. In patients with minimal and moderately advanced pulmonary tuberculosis, pneumothorax is utilized most often in the treatment of uncontrollable hemorrhage. Otherwise, it is seldom used since it is the consensus of opinion that pneumothorax should not be instituted if there is a possibility of a natural involution of the disease. Unfortunately, one cannot foretell the course of the disease in specific instances. Extension is apt to take place to uninvolved parts of the same lung or, worse still, to the contralateral lung when least expected. Indeed, this may occur in the presence of retrogression of the primary seat of the disease.[1] According to recent views,[2] pulmonary tuberculosis does not begin in the apex but more often in the infraclavicular region, the process then progressing or retrogressing quite rapidly accompanied by few symptoms and physical signs. Obviously, such an evolution makes any attempt at prognostication a hazardous one.

Since there is a paucity of reliable criteria to enable the physician to gage the course of the tuberculosis and since active disease in a young individual is a serious matter, it seems justifiable to institute pneumothorax as soon as it becomes apparent that the process in the lung is not showing signs of retrogression, particularly when cavities are present. A period of 2 or 3 months of observation with the patient under complete bed rest should suffice in the majority of instances. In patients with progressive pulmonary tuberculosis, the indication for pneumothorax is obviously a matter of urgent necessity. In the present state of knowledge of pulmonary tuberculosis and the *modus operandi* of collapse therapy, it appears that pneumothorax is the treatment of choice in young patients with relatively benign, infraclavicular or centrally located pulmonary tuberculosis if the disease does not show evidences of spontaneous resorption or cicatrization of the lesion under rest treatment.

Symptomatic improvement, particularly in the early months of treatment, is to be expected in many instances with bed rest alone although the disease in the lung may be little affected, indeed, may be progressing, simultaneously. This initial period of symptomatic improvement is apt to deceive the physician as well as the patient and pneumothorax is withheld as a consequence. Too often, subsequent recrudescence of the disease results in bilateralization or generalization of the tuberculosis and renders pneumothorax impracticable.

Two-to-fifteen-year End Results in 324 Cases. The results with pneumothorax depend on the character and extent of the pulmonary disease and on the collapse attained. This applies in a general way, but in specific instances neither factor can be estimated with any degree of accuracy. Indeed, after reviewing several hundred films, it seems that the supposedly measurable components of the pulmonary collapse are almost as immeasurable as are the factors that determine the individual's resistance to the disease. Unilateral tuberculosis in some patients, in spite of a satisfactory collapse of the lung, spreads to the unaffected lung and runs a fatal course. In others, with initially bilateral involvement, there is seen occasionally retrogression of the disease not only in the treated but also in the contralateral lung. Likewise, a pocket of air is apparently efficacious in one instance by localizing itself over an actively diseased area; a larger pocket of air in another patient may be ineffective because it collapses more of healthy than of diseased lung tissue. In any event, one is apt to judge the character of the collapse by the final outcome rather than by the results expected before the institution of the pneumothorax. At times, the outcome is such as to make one wonder as to the rôle the pneumothorax really played in influencing the evolution of the disease.

Our study of the results with therapeutic pneumothorax in pulmonary tuberculosis differs somewhat from similar studies made by others in as much as follow-up letters played a small part. Many of our patients who improved sufficiently had an opportunity to work part or full time in the Altro Shops, conducted by the Committee for the Care of Jewish Tuberculous. Here they were under medical and nursing supervision, the physical examinations being supplemented when necessary with roentgenograms. Of the patients who succumbed, 76 per cent did so in Montefiore Hospital. Many of the intermediate groups were readmitted on one or more occasions to the city hospital or the country sanatorium. A number of working patients were sent to the latter institution for vacations during the summer months. Several years ago a follow-up clinic was established where discharged patients are able to continue pneumothorax treatment and at the same time engage in various occupations. Our results are, therefore, to a considerable degree, based on first hand information of a homogeneous group of individuals whose

physical condition was ascertainable with some degree of accuracy. These end results have never before been collected for publication and are not included in Dr. Fishberg's work.

In the years 1916–1930, inclusive, 377 patients with pulmonary tuberculosis were treated with pneumothorax. With few exceptions, the disease was in an advanced stage. Information of the present condition of these patients is available in 324 instances, or in 86 per cent of the total number treated. Of this number, 13 patients are still receiving pneumothorax (2, since 1924; 2, since 1927; 1, since 1928; 3, since 1929; and 5, since 1930). Although some of the best results are to be found among the patients of this group, they are not included in estimating the final results. Likewise, 18 patients who have stopped receiving pneumothorax in the years 1931 and 1932 are also excluded. An interval of at least 2 years should elapse after pneumothorax is discontinued before one attempts to evaluate the results of the treatment.

The table summarizing the results with pneumothorax at Montefiore Hospital and Country Sanatorium is given with the full realization of the many shortcomings that enter presentations in which the personal equation plays such a decisive part. Nor does a multiplicity of tabulated data solve the problem. It is just as apt to confuse as to clarify matters. To reduce sources of error to a minimum, the material is arranged according to predominance of unilaterality or bilaterality of disease and according to whether or not the pneumothorax, irrespective of its character, could be maintained for a period of at least 3 months (Table 1). The majority of the patients who received treatment for less than 3 months were essentially instances of frustrated attempts to establish a pneumothorax either as a result of pleural adhesions (predominantly unilateral group) or as a result of the *ultimum refugium* type of patient (predominantly bilateral group) in whom collapse of the more actively diseased lung was tried on the principle that there was nothing to be lost by the attempt. Rarely was there anything gained. That a considerable number of our patients fell into the hopeless group may be gathered from the fact that no less than a third of all the fatal instances occurred within 6 months of the time of induction. Needless to say, comparatively few of those who received pneumothorax for more than 3 months sustained complete collapse of the affected lung.

Pneumothorax for at least 3 months was given to 143 patients with predominantly unilateral pulmonary tuberculosis. Of these, approximately 28 per cent are clinically arrested and 13 per cent are improved to a degree that a number are working or able to work. It should be noted that among the improved group of patients the sputum of 8 became negative and that some patients remained well for as long as 15 years. They are not included among the clinically arrested group because there was insufficient proof that

such was the case. Our positive results in patients with predominantly unilateral pulmonary tuberculosis in whom some degree of pneumothorax could be established constitutes roughly about $\frac{1}{3}$ of the patients treated. The stationary group of patients includes many who were symptomatically benefitted by the treatment but who subsequently needed further hospitalization or additional

TABLE 1.—TWO- TO FIFTEEN-YEAR END RESULTS IN 324 CASES, 1916–1930.

Condition *	No	Predominantly unilateral pulmonary tuberculosis		Predominantly bilateral pulmonary tuberculosis	
Still receiving PNX	13	3 mos. or more	Less than 3 mos.	3 mos. or more	Less than 3 mos.
Discontinued 1931 and 1932	18				
Clinically arrested	44	41	1	2	0
Sputum negative	35				
No sputum	5				
Sputum unknown	4				
Improved	23	19	0	4	0
Sputum negative	8				
Sputum positive	2				
No sputum	7				
Sputum unknown	6				
Stationary	18	14	2	0	2
Progressive	11	4	1	5	1
Uncertain	5	4	1	0	0
Dead†	186	61	42	31	52
Within 3 mos. of induction, 30					
Within 6 mos. of induction, 59					
Within 1 yr. of induction, 88					
Within 2 yrs. of induction, 141					
Within 5 yrs. of induction, 174					
Total	318	143	47	42	55
* Bilateral PNX, not analyzed	3				
† Non-tbc. causes, not analyzed	3				
	324				

collapse procedures. There are relatively few patients in the progressive group for the reason that not many are alive after a lapse of 2 years. Sixty-five per cent of all the patients treated had effusions of varying degree detectable roentgenologically during the course of treatment. In about 40 per cent of all the patients treated, the effusion occupied $\frac{1}{3}$ or more of the pleural cavity. The presence of a

pleural effusion seems to have had no effect on the final outcome. Among the 143 patients with predominantly unilateral pulmonary tuberculosis who received pneumothorax for 3 months or more, the incidence of pleural effusion among the patients whose disease became arrested and among the patients who died was approximately the same, 80 to 78 per cent. These comparative findings support the belief that pleural effusions in the course of the pneumothorax should not be aspirated unless pressure symptoms or other urgent indications arise. In several instances when a partial pneumothorax was followed by an effusion, the prognosis was distinctly improved as a result. More often, however, our statistics as to the ultimate effects of such effusions notwithstanding, their appearance caused

TABLE 2.—COMPARATIVE RESULTS WITH THERAPEUTIC PNEUMOTHORAX IN 1926 CASES, REPORTED BY 10 DIFFERENT OBSERVERS.

Source	Type of material	Period of observation, years	Number	Living	Per cent	Dead	Per cent	Results of total number, per cent
Münchbach[3]		2–9	475	273	57	202	43	Fully able to work, 37.
Gravesen[4]	PNX practicable	2–12	140	60	43	80	57	Able to work, 39.
Roloff[5]	Simple unilateral PNX, 6 mos. or longer	2–12	262	*	60	*	40	Sputum negative, 45.
Macnal[6]		2–12	172	85	49	87	51	Fully able to work, 36.
Peters[7]	Satisfactory or incomplete effective collapse; exclusive of those under treatment	2–14	167	79	47	88	53	Condition satisfactory, 30.
Arna[8]	Successful PNX	2–14	170	46	27	124	73	Fully able to work, 21.
Zinn and Siebert[9]	Partial or total PNX	2½–15	183	77	42	106	58	Healed, 15.
Hurrell[10]	Successful PNX induced	3–10	99	27	27	72	72	Well, 17.
Schröder[11]	Av. duration of PNX, 8½ mos.	3–15	115	50	44	65	56	Healed, 37.
Rubin	Predominantly unilateral: PNX 3 mos. or more	2–15	143	82	57	61	43	Clinically arrested, 29; sputum negative, 30.
Total	More or less PNX induced	*	1926	779	47	885	53	

premature abandonment of pneumothorax treatment. About 16 per cent of all the effusions were purulent in nature. The prognosis of patients with pyopneumothorax, with few exceptions, is a gloomy one.

The results in this series when compared with those reported from other institutions (Table 2), reveal a striking similarity in accomplishment. The minor variations are due to differences in the types of patients treated and interpretations of results rather than to any specialized modifications in treatment. Of major importance is the interval that is allowed to elapse between the time of discontinuation of pneumothorax treatment and the assessment of the results. The longer this interval the worse appear the final results. After a lapse of at least 2 years, about 25 per cent of the patients are in good condition without tubercle bacilli in the sputum and

able to work; about 25 in fair condition and about 50 per cent dead. These percentages, as is true of statistics in general, do not represent the actual facts. Obviously, one cannot expect permanent benefits of the treatment in patients with bilateral pulmonary tuberculosis or when pleural adhesions prevent collapse of the cavities in the lung. Yet, this applies to a large number of patients treated with pneumothorax. Symptomatic improvement is the most that can be expected under such conditions. Equally deceptive, on the other hand, are the unusually favorable results obtained in patients with unilateral disease in whom the pneumothorax caused complete collapse of the cavities and in whom the treatment could be maintained for several years and discontinued voluntarily. Such selected groups of patients constitutes a relatively small minority of all the patients treated. The results are significant in so far as it demonstrates the value of collapsing tuberculous cavities. It is very likely that with the change in views regarding the indications for pneumothorax treatment, in time, many more patients will fall into the latter group.

Conclusions. Pneumothorax improves the condition of many patients with pulmonary tuberculosis who otherwise would very likely not have done as well. Quite infrequently, collapse of the lung, even when partly successful, helps the individual to arrest the progress of the disease so that he becomes economically rehabilitated and is able to lead a normal although somewhat sheltered life. The individual, however, is still tuberculous and subject to all the vicissitudes of the disease. At the present time in comparatively few does it result in full clinical recovery in a sense that the tuberculous process undergoes absorption or complete fibrosis and calcification. It is hazardous to speak of cure, under any condition, when reactivations are liable to occur at any time during the life of the patient. Pneumothorax attempts to treat pulmonary tuberculosis, not the tubercle bacillus. For this reason, if for no other, such a measure directed locally in the treatment of this condition is necessarily limited in its sphere of action.

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THE BEHAVIOR OF THE DIAPHRAGM AFTER PHRENICO-EXAIRESIS.

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The therapeutic effects of phrenicoexairesis in pulmonary tuberculosis, irrespective of the character, extent, and location of the lesion, depend on the changes produced by the procedure in the position and function of the corresponding hemidiaphragm. Successive examinations of the paralyzed muscle are therefore of considerable prognostic value, and often serve to explain the failures as well as the successes of the treatment.

In chronic pulmonary phthisis varying degrees of impairment of the normal function and, occasionally, complete immobility of the hemidiaphragm on the more diseased side are not uncommon. Even more frequently we meet with a position of the hemidiaphragm higher than normal on the side of the contemplated operation. Occasionally, the upward retraction, resulting from fibrosis and contraction of the lung, is greater than the rise which could be expected from a radical phrenic nerve interruption.

Although there are no definite criteria by which the results of phrenicoexairesis can be foretold, these abnormalities yield much valuable information in regard to the possibilities of an effective postoperative rise of the hemidiaphragm. Not only for this reason, but also for comparative purposes is it important that the function and position of the diaphragm should always be determined before operation.

Examination of the Diaphragm. Various landmarks have been proposed whereby to measure the postoperative rise of the diaphragm on the roentgenogram. Most of them are unsuitable because their positions vary too much with different examinations. The method employed in the 170 cases studied in this series consists in determining the difference between the positions of the two halves of the diaphragm by means of horizontal lines drawn through the highest points of the domes before operation, and adding the figure thus obtained to, or subtracting it from, the difference in the positions of the two domes after operation, depending upon whether the hemidiaphragm on the operated side was originally lower or higher than on the contralateral side. The rise may also be measured by the difference in the distance between the tip of the transverse process of the first thoracic vertebra and the highest point of the dome of the hemidiaphragm, before and after operation (Figs. 1*a* and 1*b*). Although subject to error, owing to the inconstant heights of the

normal and of the paralyzed hemidiaphragms in films taken at different times, these measurements are more accurate than recording the elevations in interspaces and fingerbreadths.

On fluoroscopic examination the paralyzed hemidiaphragm is either immobile, or presents a paradoxical motion (a rise of the diaphragm instead of a descent with inspiration, and the opposite with expiration). The latter may be absent on ordinary respiration, but may be brought out in many cases by the sniffing test and the Bittorf[1] test. The sniffing test is performed by having the patient inspire forcibly through the nose with the lips tightly closed; and the Bittorf test, by a strong inspiratory effort with the lips and the nostrils tightly closed. The result in both tests is a rise of the hemidiaphragm with inspiration, and a descent with expiration. Frequently the paradoxical motion produced by these tests is more marked than the paradoxical motion on ordinary respiration. They may, however, be absent even when the paralysis is complete.

TABLE 1.—RELATIONS BETWEEN ACTUAL, MINIMUM, MAXIMUM AND AVERAGE RISES OF THE DIAPHRAGM, AND LENGTH OF NERVES EVULSED IN 138 CASES.

Rise of diaphragm in cm.	Length of evulsed nerve in cm.							Total	Per cent.
	2.5–5.5	6–9	10–15	16–20	21–30	31–38	Over 38		
No rise	6	3	1	1	..	1	..	12	8.8
1–2	..	1	..	..	1	..	..	2	1.4
2–3	2	3	2	3	3	3	..	16	11.7
3–4	4	10	11	2	4	2	1	34	24.8
4–5	1	3	5	4	8	4	..	25	18.2
5–6	1	2	6	3	7	4	..	23	16.8
6–7	1	1	1	..	6	1	1	11	7.8
7–8	..	1	3	..	1	2	1	8	5.6
8–9	..	..	1	..	3	..	..	4	2.8
9–10	..	..	..	..	2	..	..	2	1.4
11–12	..	..	..	..	..	..	1	1	0.7
Average rise	3.87	3.79	4.54	3.85	5.16	4.67	5.02		
Minimum rise	2.00	1.25	2.00	2.00	1.20	2.00	3.10		
Maximum rise	6.60	7.50	8.75	5.00	9.00	7.70	7.50		
Average rise rt.	4.31	3.54	4.35	3.89	4.70	5.85	4.55		
Average rise lt.	3.00	4.07	4.67	3.73	5.55	4.50	5.50		
Maximum rise rt.	6.60	4.20	7.20	5.00	9.00	7.70	6.00		
Maximum rise lt.	3.10	7.50	8.75	5.00	8.75	7.00	7.50		

I. *Changes in the Position of the Diaphragm.* The effect of phrenic nerve interruption on the position of the corresponding hemidiaphragm has been studied in a series of 170 cases. In 12 cases the position of the hemidiaphragm could not be determined on account of opacity of the lung field, and 20 cases were not included for various other reasons.

In 12 (8.7 per cent) of the 138 cases thus available for study, no rise of the hemidiaphragm occurred (Table 1). Some authors have reported a much greater proportion of such cases. Frank and Miller[2]

found no ascent in about 30 per cent of 85 cases. Cooper[3] reported no rise in 36.8 per cent of 103 cases. Others, however, found no rise, in the presence of paralysis, in a very small proportion of cases. Edwards[4] observed it only three times in 98 cases, and Broga and Welles[5] in 3 out of 72 cases.

In 4 cases the failure of the hemidiaphragm to rise was due to the fact that no paralysis of the muscle was produced by the procedure. In 2 the hemidiaphragm showed complete immobility throughout a period of observation of 3 months and 5 years, respectively. In 1 case the hemidiaphragm was completely immobile before operation. One case presented a marked paradoxical motion during a period of observation of 6 months. In 3 cases the function of the hemidiaphragm was not noted, but no rise had occurred 9 months, 1 year and 2 months, and 1 year and 4 months, respectively, after operation. In 1 case, crushing of the nerve produced no result. Five months later an exairesis of 31.25 cm. was performed. One month later there was no rise, with an immobile hemidiaphragm.

No relation could be established between failure of the hemidiaphragm to rise and the extent of nerve resection, in view of the fact that other cases with the same lengths of nerve evulsed showed elevations from 2 to 7.5 cm. The paralyzed hemidiaphragm may remain permanently at its preoperative level irrespective of the length of nerve evulsed. In 1 case no rise occurred after resection of 20 cm., and in another case of 31.3 cm.

The average and maximum rises of the hemidiaphragm vary considerably in different series of cases. The figures reported by various authors cannot be compared because of a lack of standard methods of measurements, and of data concerning the time between the date of operation and the date of final observation.

Of our cases 126 showed rises between 1.2 and 9 cm., with an average rise of 4.5 cm., not including 1 case in which the elevation reached 11.3 cm.

According to Thomsen,[6] Zadek and Sonnenfeld,[7] and others, there is no relation between the length of nerve evulsed and the degree of ascent of the hemidiaphragm. On the other hand, it is claimed that the probability of attaining a good rise grows with the extent of nerve removed, and that the average elevation is greater following evulsion than simple phrenicotomy. Felix[8] found an average rise of 3.7 cm. on the right and 2.5 cm. on the left after simple phrenicotomy, and 7.6 cm. on the right and 5.9 cm. on the left following exairesis, and Alexander[9] an average rise of 2.15 cm. after simple phrenicotomy and 4.25 cm. after exairesis. Sultan[10] stated that frequently, but not regularly, the height attained by the paralyzed hemidiaphragm is in direct proportion to the length of nerve removed.

An analysis of our cases shows, first, that in individual cases

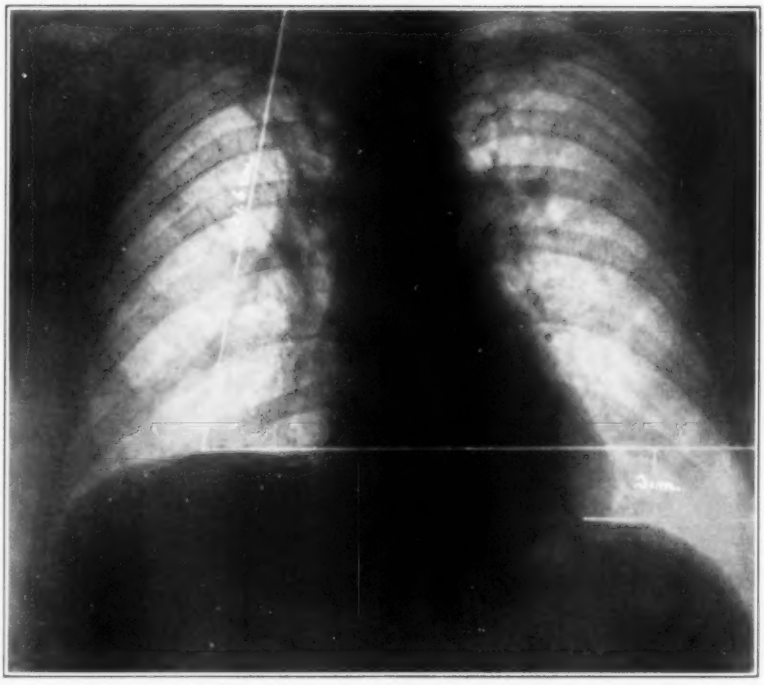

FIG. 1*a*.—Right hemidiaphragm before operation 3 cm. higher than left.

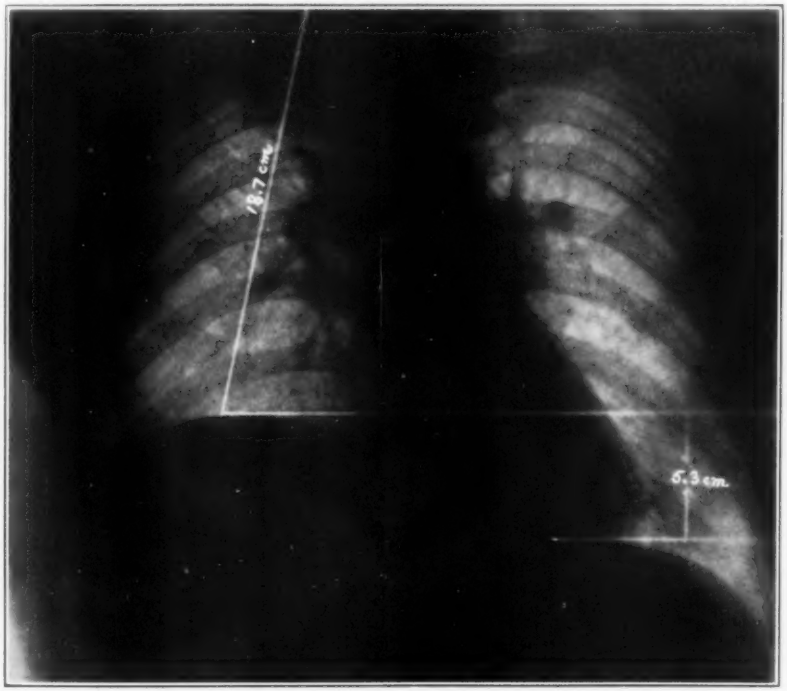

FIG. 1*b*.—Right hemidiaphragm after operation 5.3 cm. higher than left. Actual rise 2.3 cm.

higher rises may occur with resection of nerve lengths corresponding to simple phrenicotomy than with exairesis up to the whole nerve, second, that the average rises in the nerve length groups as classified in Table 1 do not permit the deduction that there is a direct relation between nerve length and degree of rise. If, however, the cases are divided into those with resection of nerve lengths less than 10 cm., and over 10 cm., the latter group shows a slightly higher average, but not great enough to justify any generalization.

Extremely high rises are not frequent. Sultan[10] has seen an elevation of the right diaphragm 11 cm. higher than the left, and of the left diaphragm 9 cm. higher than the right. Puder[11] reported a case in which the hemidiaphragm rose to the second rib. Campbell[12] found the maximum rise 8 cm. on the right and 6 cm. on the left. Maendl and Schwartzmann[13] saw an elevation of 11 cm. in 100 cases. Matson[14] found a rise of 8.5 cm. on the right side 1 year after operation, and of 13 cm. on the left side 2 years after operation, in a series of 150 cases. The maximum elevation noted by O'Brien[15] in 500 cases was 9 cm. Cooper[3] observed rises of 7 and 8 cm. Frank and Miller[2] saw elevation up to the third rib in some of their cases. In our cases the maximum rises were 9 cm. on the right side in 2 cases, 6 months, and 3 years and 5 months after the operations, and 11.5 cm. on the left side, 2 years and 4 months after operation.

Sauerbruch,[16] Felix,[5] Alexander,[9] Sultan,[10] Davies,[17] Campbell,[12] Moore[18] and others have noted that the rises on the right side are greater than on the left side, the average differences varying between less than 1 cm. and 4 cm. The explanation is that on the right side the ascent of the hemidiaphragm is aided by the upward push of the liver, while on the left side the heart hinders the rise. Thomsen[6] and Edwards,[4] on the other hand, have not been able to corroborate this observation, and have found very little, if any, differences between the two sides. In our cases, contrary to the generally reported findings, the average rise on the right was 4.3 cm., and on the left side 4.7 cm. In only 3 of the groups (Table 1) were the average and maximum rises greater on the right than on the left side. It was also found that whereas rises of 5 to 9 cm. constituted about 28 per cent of the right-sided cases, they were noted in about 43 per cent of the left-sided cases.

The probability of obtaining a rise of the hemidiaphragm is somewhat greater for the right than for the left side. Cooper[3] found that the number of right-sided cases with a rise was about 16 per cent higher than of the left-sided cases. In our cases the advantage of the right over the left side was only about 8 per cent.

The maximum elevations of the paralyzed hemidiaphragm are reached at varying periods of time after operation. Rises up to 7 cm. in from 1 week to 1 month occur frequently. In many cases the highest rise is reached within the first 6 months. Frequently, the rise increases for much longer periods of time. However, taking our

whole series of cases, it appears that the elevation bears no consistently direct relation to the time elapsed after operation (Table 2).

TABLE 2.—RELATIONS BETWEEN LENGTHS OF TIME ELAPSED AFTER OPERATION, AND ACTUAL, MAXIMUM AND MINIMUM RISES OF THE DIAPHRAGM IN 125 CASES.

From date of operation.	Number cases.	Rise of diaphragm in cm.						
		Less than 2.5	2.5–5.0	5.0–7.5	7.5–10.0	10.0–11.25	Maximum rise.	Average rise.
Less than 3 mos.	18	1	12	4	1		6.0	4.2
3–6 mos.	12	..	10	2			5.6	4.1
6–9 mos.	20	2	10	6	2		9.0	4.8
9–12 mos.	18	2	10	6			6.6	4.1
1–2 yrs.	41	4	18	15	4		8.8	4.8
2–3 yrs.	12	2	6	4			7.2	4.3
3–4 yrs.	4		1	1	2		9.0	6.8

Case with rise of 11.25 cm. not included.

In some cases we have observed the opposite phenomenon, namely, a gradual descent of the hemidiaphragm following a continuous rise, in the presence of complete paralysis of the muscle. We have seen no mention of this in the literature. In some instances the decreases were slight, and could, perhaps, be explained by differences in the positions of the two halves of the diaphragm during different exposures. In 6 cases, however, the descent varied between 2 and 3 cm., and was noted on successive examinations. The interval between the time when the maximum rise and the drop were noted was between 3 and 7 months, and in 1 case, 1 year. A fully satisfactory explanation is not offered. The descent may be the forerunner of a restoration of normal function. In the majority of the cases, however, such lengths of the nerve were evulsed which very rarely are unsuccessful in producing complete and permanent paralysis. It is probable that decrease of the intraäbdominal pressure as a result of weakening of the abdominal musculature from progressive emaciation and asthenia is an important factor in the mechanism. Similarly, no satisfactory explanation is available for the observation of varying degrees of elevation of the paralyzed hemidiaphragm at different times. In some of these cases the changes were of such an extent that they could not be ascribed to differences in the depths of the inspirations during different exposures.

Discussion. From the foregoing analysis it appears that the postoperative position of the paralyzed hemidiaphragm is not determined to any important degree, if at all, by the length of nerve evulsed. Primarily, it is the result of the combined action of the suction force of the negative intrathoracic pressure, and of the upward push of the positive intraäbdominal pressure. This mechanism, however, is supplemented and modified by the changes which take place in the structure of the muscle, and by the pathologicoanatomical character of the pleuropulmonary lesion.

Failure of the paralyzed hemidiaphragm to rise and limitation of the rise have been ascribed to fixation of the basal portion of the lung and, especially of the costophrenic sinus, by pleural adhesions. It is doubtful, however, that this plays the important rôle that has been assigned to it. According to Kahn,[19] the degree of rise depends by far more on the intraäbdominal pressure. The higher the latter, the higher the hemidiaphragm will rise. In asthenic individuals with a poorly developed musculature, and a slight amount of intraabdominal fat the pressure is very slight and a high elevation does not occur, except in a small number of cases in which there is a well developed abdominal musculature in the presence of asthenia.

In a large number of our cases phrenicoexairesis was performed because of a completely adherent lower lobe in artificial pneumothorax. Yet, in the great majority of these cases satisfactory, and even maximum rises, occurred. We have also observed cases with definite obliteration of the costophrenic angle, in which the diaphragm ran from within outward and upward in a more or less straight line, where, however, a continuous rise up to 5 cm. took place.

It is probable that the character of the lesion of the lower lobe is of greater significance in determining the ascent of the hemidiaphragm. Massive infiltration and marked fibrotic changes, which make the lung rigid and unyielding, will prevent or restrict the rise. Compensatory emphysema of the lower lobe in cases of chronic upper lobe lesions will act similarly. The most important, however, of the various factors which interact in determining the postoperative position of the hemidiaphragm, is the rapidity and intensity with which the pulmonary lesion contracts, as healing takes place, and the muscular fibers of the diaphragm undergo degeneration and atrophy. As a result of the traction and contraction of scar tissue, the intrathoracic pressure may attain high negative values whereby the hemidiaphragm may be pulled upward with great force. Degeneration and atrophy of the paralyzed muscle converts it into a thin, yielding connective-tissue membrane which offers less and less resistance to the intraäbdominal and intrathoracic pressures, and to the contraction of the lung, unless counteracted by factors which prevent or limit the ascent.

II. *Functional Changes.* For the study of the functional changes of the paralyzed hemidiaphragm there were available 112 cases with periods of observation of 3 months and longer. The number of fluoroscopic examinations made in each case varied between 2 and 14, as follows:

Number of cases.	Number of examinations.
38	2
13	3
16	4
9	5
11	6
18	7
3	8
2	9
1	10
1	11

The conditions noted were, first, lasting immobility; second, immobility which gave place to paradoxical motion; third, lasting paradoxical motion, and, finally, paradoxical motion which was replaced by immobility. In 6 cases the hemidiaphragm eventually regained its normal function.

In 52 (46.4 per cent) of the cases, the hemidiaphragm became immobile soon after operation, and remained fixed for periods of observation varying between 3 months and over 5 years.

In 14 (12.5 per cent) of the cases, the immobile hemidiaphragm developed paradoxical motion. The time after operation when the immobility was last observed was from 2 weeks to 4 months after, in 10 cases; and from 1 year and 2 months to 1 year and 7 months in 4 cases. The first observation of paradoxical motion was made from 1 to 10 months later, the average being about 3½ months.

Three cases showed complete immobility before operation. In 1 of these the hemidiaphragm remained fixed without at any time becoming elevated; in 2 paradoxical motion set in 1 month and 9 months, respectively, after operation; and in both, elevation of about 4 cm. took place, in 1 before and in the other after the paradoxical motion developed.

In 2 cases there was a return to normal function after an initial period of immobility.

Immobility, as here spoken of, refers to complete absence of respiratory excursions of the hemidiaphragm on ordinary and even deep breathing. The sniffing and Bittorf tests, however, may show paradoxical motion. Out of the 52 cases with persistent fixation, the tests were performed in 22, and were positive in 12 (54.5 per cent). In the 14 cases in which immobility was followed by paradoxical motion, the tests were positive in 13 (92.8 per cent). Comparing the two groups, it was found that, generally, the intensities of the tests were greater in the second group, and that they increased after the setting in of paradoxical motion.

In 41 (36.6 per cent) of the 112 cases, there was paradoxical motion from the start. In 3 of these the function became normal, and 4 cases are not included because the periods of observation were less than 2 months.

In 23 of the 41 cases (51.2 per cent), the paradoxical motion persisted and was positive at the termination of observation from 3 months to 3 years after operation. In 11 (26.8 per cent) the hemidiaphragm eventually became immobile. The paradoxical motion, in the latter cases, persisted for 1 to 10 months, or at an average of less than 4 months in 9 cases, and for over 1 year in 2 cases, after operation. The hemidiaphragm was found fixed from 2 to 18 months, or at an average of about 11 months, after operation. The sniffing and Bittorf tests were investigated in 16 of the 23 cases and in 10 of the 11 cases, and were found to be positive in all the former, and in 80 per cent of the latter. These findings, in connection with the results in the group where paradoxical motion followed a period of fixation, showed that although these tests are positive in a large proportion of cases with an immobile hemidiaphragm, they are practically always present when there is paradoxical motion on ordinary respiration.

Discussion. Immobility, either from the beginning or setting in after a varying period of paradoxical motion, may be considered the rule after phrenic nerve interruption, with or without a rise of the paralyzed hemidiaphragm. It was found in 63 of 100 of our cases. Frank and Miller[2] noted immobility of the hemidiaphragm in 58 (85.3 per cent) of 68 cases.

Complete fixation has been ascribed to the presence of pleural adhesions. It appears to the writer that such an explanation alone cannot be sustained. Pleural adhesions of the basal portion of the lung, so pronounced as to interfere completely with the mechanism which produces paradoxical motion, should also prevent a rise of the hemidiaphragm, or restrict it greatly. As a matter of fact, only 4 out of 52 cases in this group presented no rise. The other cases showed an average rise which was approximately the same as the general average rise. The predominating cause of immobility of a paralyzed and atrophied hemidiaphragm is, essentially, the same as that which determines the degree of elevation, namely, the character and the retractile capacity of the pulmonary process. When the retractile capacity of the lung as a result of massive infiltration and pleural adhesions is not sufficient to allow free play to the suction force of the intrathoracic pressure and to the upward push of the intraäbdominal pressure during inspiration, the hemidiaphragm will remain fixed. Where immobility gives place to paradoxical motion it must be assumed that there has occurred a change in the retractile capacity of the lung in the sense of an increased elasticity, corresponding to healing and fibrosis. Another explanation for the latter phenomenon is that the diaphragm atrophies gradually.

The farther the conversion into a lax, fibrous membrane has progressed, the more easily it is acted upon by the intrathoracic and intraäbdominal forces. The change from paradoxical motion to immobility is to be explained by the assumption that the lung becomes more and more inelastic and unyielding, and that, in addition, there occurs the development of more extensive and firm adhesions.

Paradoxical motion is produced by the upward suction of the increasing negative intrathoracic pressure during inspiration, supplemented by the increasing intraäbdominal pressure, acting upon a hemidiaphragm which has lost its tonus. Theoretically, the more marked the paradoxical motion, the more it presupposes comparative freedom from adhesions and, especially, an elastic retractile lower lobe. Practically, however, it is not true in all cases, nor even in the majority of cases. As a matter of fact it is difficult, if not impossible, to explain on the basis of the factors which are supposed to determine the presence or absence of a rise of the hemidiaphragm, and of paradoxical motion, why the latter is marked in some cases and absent in others.

Although in individual cases no relation between the degree of rise and the presence of lasting paradoxical motion can be established, this group as a whole shows a higher average rise than the other groups, and than the general average rise. There also does not appear to be any relation between the length of nerve evulsed and paradoxical motion or immobility.

The degree of paradoxical motion on ordinary respiration, and by the sniffing and Bittorf tests, bears a fairly definite proportional relation to the time elapsed after operation, due to the increasing degeneration of the muscle fibers. It is borne out by an analysis of our cases, which showed a higher average rise, by about 3 cm., in the group with moderate and marked paradoxical motion than in the group in which it was classified as of slight degree. Only 1 of the cases with paradoxical motion of a marked degree showed no rise of the hemidiaphragm during 8 months after operation and evulsion of 7.5 cm. of the nerve.

Summary. The changes in the function and position of the hemidiaphragm after phrenic nerve interruption have been studied in a series of 138 cases.

The characteristic effects of phrenicoexairesis on the diaphragm are a rise of the muscle into the thoracic cavity, immobility, and paradoxical motion.

In a small proportion of cases the hemidiaphragm remains permanently at its preoperative level, even after evulsion of a sufficient length of nerve to produce complete and lasting paralysis.

In the majority of cases, there occurs a rise, which in the largest number of these is associated with immediate or subsequent lasting immobility of the hemidiaphragm.

Failure of the paralyzed muscle to rise, the degree of rise, immobility and paradoxical motion, all depend largely if not entirely on the character of the pulmonary process, especially of the lower lobe, and on the extent and character of pleural adhesions, especially of the basal portion.

The mechanism by which all these conditions are determined, however, requires further physiologic and pathologico-anatomical study.

The effect of phrenicoexairesis on the pulmonary lesion is determined largely by these changes. A study of the behavior of the phrenicectomized hemidiaphragm in every case is therefore important from a prognostic standpoint.

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THE EFFECT OF PREGNANCY ON THE INSULIN REQUIREMENT OF THE DIABETIC.

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There are conflicting views regarding the effect of pregnancy on the insulin requirement of the diabetic. This is due largely to the infrequency of pregnancy in the diabetics who require insulin; there was not a single instance of diabetes in 27,567 consecutive patients confined in the City of London Maternity Hospital.

The purpose of this paper is to clarify existing misunderstanding in regard to changes in the insulin need and to formulate, if possible, certain rules, the adoption of which, we believe, will minimize the risk to the mother and child.

Since the observations of Carlson and Drennan[1] an improving tolerance during the last months of pregnancy has been attributed to insulin supplied by the pancreas of the fetus. That this may actually occur is beyond doubt. One of Wilder's[2] patients became diabetic, requiring insulin in the first trimester of pregnancy while in the last trimester the insulin was discontinued, to be resumed after the nursing period was over. The third case in the same publication behaved in a similar fashion. Gray and Feemster[3] report a great economy of insulin after the 8th month of pregnancy. At necropsy a remarkable hypertrophy and increase in the number of islets in the baby's pancreas were found. Others[4-11] report a reduced insulin need or improved food tolerance in the last trimester of pregnancy.

When evidences of a rapidly gaining tolerance present themselves there is no alternative but to reduce the insulin or increase the diet. The question arises: is the abnormal output of insulin by the fetal pancreas a compensatory affair, the result of an unusual demand—poorly controlled diabetes in the mother—if so, can we prevent this hyperfunction with its possible injury to the child by keeping the maternal blood sugar normal?

This was the aim in our 6 cases. Even though the renal threshold is lowered in pregnancy,[12] every attempt was made to prevent glycosuria. In none was there evidence of assistance from the fetal pancreas. We are inclined to attribute this to the exact control of the diabetes and believe that if we had been less fortunate in this respect that compensatory activity of the fetal pancreas would have been more likely.

It is generally agreed that carbohydrate tolerance is lost during the first 3 months of pregnancy, the period of greatest metabolic readjustment. This has been our experience also. Judging from the literature, it is apparent that the second trimester is freest from complications. In our cases the insulin requirement remained stationary during this, the period of greatest qualitative fetal development. Unlike the results of others referred to above, we noted that each patient during the final trimester, the one of greatest increase in body mass, required increasing quantities of insulin. Two patients reported by Collens and Shack[13] illustrate this change. Bowen and Heilbrun[14] in reporting 5 cases showed evidence of loss of tolerance in 3. Their review of 43 cases from the literature revealed an increased demand for insulin in 28 and a decrease in 10. Of Peckham's[4] cases, 3 (6, 9 and 12) lost tolerance during pregnancy. This was true of 1 patient reported by McIlroy, Hill and Pillman-Williams.[15] Others[2,7,16-35] report instances of loss of tolerance in the last trimester. It would appear that more lose tolerance than gain it during pregnancy.

We have collected 78 pregnancies complicating diabetes from the literature and have added the 6 reported in this paper. These cases comprise all of those, to the best of our knowledge, in whom the insulin requirement was sufficiently clear to enable us to determine the effect of pregnancy upon it. The results of this survey are presented in Table 1.

TABLE 1.—THE EFFECT OF PREGNANCY ON THE DIABETIC'S TOLERANCE AS JUDGED BY CHANGES IN THE AMOUNT OF INSULIN REQUIRED.

The diabetic's tolerance during pregnancy	No. of cases	Per cent total
I. Impaired (no evidence of hyperactive fetal pancreas)	47	55.9
II. Unchanged (possibly some assistance from fetus)	16	19.1
III. Improved (evidence of hyperactive fetal pancreas)	21	25.0
	84	100.0

Case Reports. CASE 1.—Mrs. T. A., aged 38, height 63 inches, weight 117 pounds (53 kg.), had diabetes since 1924. Insulin was begun in April, 1925. The patient gave a history of 1 previous pregnancy. The baby died at 2 weeks of age. Except during the first pregnancy, there had been no disturbance in menstruation. Her mother had glycosuria of undetermined cause. The only past illness was scarlet fever in childhood. Her general physical condition was excellent. The pregnancy began in September, 1927. Before this time her daily dosage of insulin was 40 units, at the end of the 3d month it was 82 units, at the end of the 6th month 82, and at the end of the 9th month 98. Following a normal delivery there were severe insulin reactions and the insulin requirement dropped at once to 44 units. The baby weighed 9 pounds, 6 ounces.

CASE 2.—Mrs. M. (Physiatric Inst. Case 385), aged 30, with recognized diabetes since 1919, gave a family history (father) of diabetes. Insulin was begun in 1923. Her weight was normal and showed no unusual change. Prior to the pregnancy in 1924 she required 72 units of insulin daily, at the end of the 3d month 78 units, at the end of the 6th month 78, and at the end of the 9th month 100. Subsequent to delivery the requirement was 72 units.

CASE 2.—Second pregnancy. Prior to the second pregnancy in 1927, the daily insulin need was 72 units, at the end of the first trimester 76, of the second trimester 76, and of the third, 100. Her standard dosage following delivery proved to be 70 units. Severe insulin reactions followed both deliveries, making imperative reductions below the usual dosage for this patient for several days.

CASE 3.—(Physiatric Inst. Case 1914.) Mrs. N., aged 20, with a history of diabetes since 1924 and amenorrhea until 1926, became pregnant in June, 1929. Insulin had been started in 1924 and the daily dosage prior to pregnancy was 75 units. Unfortunately, we have no record of her insulin throughout the pregnancy, but at the end of the 9th month it was 94 units. Following delivery insulin reactions were prominent and the insulin was reduced to 40 units. The insulin requirement remained below her normal requirement while she nursed her baby.

CASE 4.—(Physiatric Inst. Case 2317.) Mrs. M., aged 32, had been treated for diabetes since 1923. She was married in September, 1929, and became pregnant in March, 1932. There had been no disturbance in menses since beginning insulin in 1923. Before pregnancy she required 40 units of insulin daily, at the end of the 3d month 48, of the 6th month 48, and of the 9th month 100. When standardized following delivery but while she was nursing the baby, her insulin need was 35 units. The diet remained constant throughout.

Case 5.—Mrs. J. H. R., aged 30, height 62 inches, weight 89 pounds (40 kg.), gave a family history (maternal) of diabetes. Diabetes and pregnancy were both recognized in September, 1931. Past illnesses were diphtheria, mumps and measles in childhood. Her physical condition was good except for undernutrition. Prior to the pregnancy glycosuria had never been found though tested for regularly, the patient being a laboratory technician. She did not need insulin before pregnancy; at the beginning of the 2d trimester she required 4 units daily; of the 2d trimester, 6 units and of the 3d trimester, 8. Following delivery the blood sugar remained at the lower border of normal. The insulin was discontinued and until the present (June, 1933) there has been no return of hyperglycemia or glycosuria. The mother did not nurse the baby. The baby's weight at birth was 6 pounds, 14 ounces.

Table 2.—Insulin Requirement During Each Trimester, Compared With That Before and After Pregnancy.

	Daily insulin requirement (units).					
Case	Before pregnancy.	At end of 3d mo.	At end of 6th mo.	At end of 9th mo.	After delivery.	Remarks.
1	40	82	82	98	44	
2	72	78	78	100	72	First pregnancy
2	72	76	76	100	70	Second pregnancy
3	75	?	?	94	40	Nursed baby
4	40	48	48	100	35	Nursed baby
5	0	4	6	8	0	

Comments. Six successful pregnancies in 5 diabetics are reported. In all but 1 (Case 5) in whom the menses had been normal, menstruation had previously returned under insulin and diet treatment.

In each case, changes in the insulin requirement throughout pregnancy behaved in a similar fashion and in each case a prompt decrease in the insulin need followed delivery. The diabetes was not more severe after than before the pregnancies. The 2 patients who nursed their babies needed less insulin during the nursing period than before pregnancy. This is in agreement with the observation of Macleod, Markowitz and Simpson.[36]

The babies are all living and well.

Changes in diet probably played a small part in changing the insulin requirement. The total calories were not increased though a higher carbohydrate content was allowed and was continued after confinement—after the insulin had been reduced. There was no unusual gain of weight in any of these patients.

Summary. Though the number of cases is too small from which to form absolute conclusions, we believe that:

1. Exact control of the diabetes throughout the course of pregnancy will prevent abnormal demands on the pancreas of the fetus.

2. By adopting this practice the insulin requirement increases in the first trimester, remains constant in the second, increases in the third and decreases suddenly after delivery. In consequence, it would appear that the time of greatest danger from ketosis is in

the first and third trimesters; and from hypoglycemia, immediately following delivery; whereas if the second trimester is entered free from complications there is little likelihood of trouble during this midperiod.

3. Differing from the behavior of the uncomplicated diabetic, there is in our experience a paradoxical behavior of the insulin requirement in the last trimester of pregnancy: when the insulin is increased fully to cover the needs of the diabetic, there is not a gain but a loss in tolerance; we regard a gain in tolerance at this time as unfavorable for the child as it is due in all probability to an abnormally active fetal pancreas.

4. Pregnancy under ideal conditions and treatment does not permanently impair the diabetic's tolerance.

5. Diabetes *per se* is not a contraindication to pregnancy.

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RHEUMATIC FEVER IN PIEDMONT VIRGINIA.

I. Incidence and Clinical Manifestations.*

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The apparent relationship of climate to variations in the incidence and course of rheumatic infection has commanded much deserved attention in the medical literature of the past half century. For any disease which is so obviously influenced by extrinsic physical factors should offer peculiar advantages for analysis. As early as 1859 Hirsch[1] studied the global distribution of rheumatic fever and noted its relative infrequency in tropical and subtropical countries. These observations have in the intervening years become generally confirmed by investigators from both old and new hemispheres.

The purpose of this study has been to determine, as far as is practicable, the incidence of rheumatic disease for the central piedmont section of Virginia and to note in particular the occurrence and severity of its various forms. It is fully realized that statistical values founded upon hospital admissions alone do not offer an accurate index to the morbidity of a disease which is so commonly treated in the home. Community studies, though more exact, presuppose facilities which are but rarely available. It is thought, however, that a fairly accurate respresentation of the occurrence of the *various manifestations* of rheumatic disease is afforded by detailed observation of a number of individual cases.

The extensive literature relative to the subject has been more recently reviewed by Paul.[2] It would appear that accurate information as to the true climatological incidence and severity of rheumatic disease *in all of its manifestations* is not readily obtainable from the majority of epidemiological surveys. In most instances uniform definitive criteria for the selection of cases have not been employed or not specifically stated. Increasing evidence points to a variability in the character of rheumatic disease for different geographical areas. It is, therefore, apparent that the incidence of a single

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rheumatic manifestation, such as arthritis, cannot be considered in any or all localities as an index to the occurrence of the disease as a whole. Likewise, the frequent omission of pediatric cases from the statistical study of a disease to which children are particularly susceptible would seem an obvious fault.

The concept of rheumatic fever as a general bodily infection with widespread clinical and pathologic forms has been, through repeated observations, satisfactorily established. Cheadle,[3] in 1888, recognized the association of arthritis, pleurisy, endocarditis, tonsillitis, chorea, exudative erythemata and subcutaneous nodules, urging a broader visualization of the disease. Three years before, Howard[4] emphasized the frequency of pulmonary manifestations and assembled 109 cases from the current literature in which pneumonia, pleurisy, or bronchitis had been observed. Extensive involvement of the vascular system, aside from intrinsic heart lesions, has more recently been described by Klotz,[5] by MacCallum,[6] and by Von Glahn and Pappenheimer.[7, 8] In a recently published monograph, Coburn[9] stresses the importance of a wider consideration of the "Rheumatic State—a mosaic of disease patterns."

Although the clinical and pathologic manifestations of rheumatic infection are numerous and widely varied, but few of these forms when occurring singly are characteristic of the disease. Thus arthritic disturbances, Sydenham's chorea, or a certain pattern of circulatory phenomena must be present, alone or in combination with other associated signs, before a diagnosis may be established. It would appear that in some localities these essential diagnostic figures of rheumatic disease may exist in so mild a form as commonly to escape recognition, even as in others the severity and variability of their associated manifestations often confuse the issue. Arthritis may be caused by a number of known and unknown factors, and endocarditis occurs in the absence of rheumatic infection. Continued investigations afford increasing evidence of the probable rôle of streptococcus infection as the causative agent in rheumatic disease. If true, the kinship of that condition to scarlet fever and follicular tonsillitis cannot be denied. Yet these conditions, although paralleling rheumatic fever in distribution and severity, may not be included in statistical studies of that disease unless other definite rheumatic manifestations are demonstrated in the same individuals. Likewise acute nephritis, although not proven to be characteristic of rheumatic disease, has long borne an implied association with that condition partly as a true rheumatic manifestation and partly on account of a supposed clinical and climatologic similarity. Its admission rate for the University of Virginia Hospital (0.74 per cent), based on criteria similar to that utilized below for rheumatic fever, is recorded here in the hope that further parallel observations may be stimulated. Unless associated with characteristic rheumatic manifestations, cases of

acute nephritis have been excluded from the subsequent analysis of rheumatic fever cases.

To clear away any possible doubt as to the type of case under consideration we have confined our observations to patients diagnosed as having acute or recurrent rheumatic arthritis, valvular heart disease of rheumatic origin, rheumatic carditis with or without diagnosable valvular disease and Sydenham's chorea. We have studied 200 persons so diagnosed in the medical and pediatric wards of the University Hospital, during the 6-year period from June 1, 1926, to June 1, 1932. Of this number 158 (92.5 per cent) were listed as residing in Virginia. Nine of the remaining 15 persons lived in the adjacent state of West Virginia; 6 came from more distant localities. Thus a great majority were from the central piedmont section of Virginia, with an altitude of from 500 to 1500 feet.

TABLE 1.—RHEUMATIC FEVER (ACUTE, RECURRENT AND CARDIAC FORMS AND CHOREA).

(University Hospital, University, Va., June 1, 1926, to June 1, 1932.)

	Admissions.	Rheumatic disease.	Rate, per cent.
Hospital	40,536	200	0.48
Medical and pediatric wards	14,758	200	1.35
Medical wards alone	10,686	165	1.54
Pediatric wards alone	4,073	35	

Cases have been analyzed with particular reference to the frequency and degree of the manifestations of the rheumatic syndrome in this region. Preliminary studies concerned with a comparison of the incidence and character of rheumatic infection for the piedmont and tidewater sections of Virginia would seem to indicate marked differences in the forms of the disease for these localities. Analysis of a second group of 42 patients from tidewater Virginia (Norfolk), collected over exactly the same period and arranged similarly by Dr. W. B. Martin, of Norfolk, offers interesting contrast in regard to incidence and occurrence of the various rheumatic manifestations.

In our series the admission rate for rheumatic disease as calculated for medical and pediatric admissions and medical admissions alone is given in Table 1.

For the sake of comparison, the average yearly admission rate for rheumatic disease as obtained for medical patients alone (admissions to adult medical wards) has been computed (Table 2), modified from the reports of Faulkner and White,[10] of Longcope,[11] and of Harrison and Levine.[12] The percentage obtained for central piedmont Virginia (1.54) would appear to indicate that the disease occurs as commonly in this locality as in Baltimore, for Longcope in the selection of medical cases employed criteria similar to those utilized in this study. Yet a single previous figure quoted from Richmond, Virginia, by Harrison and Levine indicates a far

lower frequency. This discrepancy is due partially to the failure to include all rheumatic manifestations in the Richmond figure and partially to probable actual difference between the frequency of rheumatic fever in eastern and central Virginia. This latter explan-

TABLE 2.—RHEUMATIC DISEASE: REGIONAL DISTRIBUTION.

(Adapted from Faulkner and White, and Longcope.)

Locality.	Av. yearly med. adm.	Av. yearly adm., rh. fever, chorea.	Rate, per cent.
San Francisco Hosp., Calif.	1,255	47 0	3 75
Sacred Heart Hosp., Spokane, Wash.	1,384	42 0	3 03
Univ. Hosp., Iowa City	1,537	38 0	2 40
Univ. Hosp., University, Va.	1,781	27 5* †	1 54
Bellevue Hosp., N. Y.	25,915	375 0	1 50
Johns Hopkins Hosp., Baltimore	1,723	23 0*	1 37
Peter Bent Brigham Hosp., Boston	2,480	31 0	1 30
Hosp. of Univ. of Penna., Phila.	1,518	17 0	1 20
Univ. Hosp., Omaha, Neb.	760	5 0	0 70
Charity Hosp., New Orleans	5,349	28 0	0 52
Jefferson Hosp., Philadelphia	4,085	19 0	0 50
Barnes Hosp., St. Louis	1,338	6 5	0 47
Los Angeles County Hosp.	13,614	55 0	0 44
Baptist Mem. Hosp., Memphis, Tenn.	3,037	6 5	0 20
Univ. Hosp., Augusta, Ga.	2,500	2 0	0 08

(Adapted from Harrison and Levine, 1924.)

Locality.	Av. yearly med. adm.	Av. yearly adm., rh. fever.	Rate, per cent.
Peter Bent Brigham Hosp., Boston	1,593	30 0	1 85
Barnes Hosp., St. Louis	1,319	14 0	1 04
Galveston Hosp., Galveston, Tex.	875	7 0	0 84
Johns Hopkins Hosp., Baltimore	1,911	14 0	0 73
Charity Hosp., New Orleans	6,632	18 0	0 30
Richmond, Private practice, Dr. VanderHoof	1,332	1 0	0 07

* Includes cases of acute and recurrent rheumatic fever, rheumatic heart disease and chorea.

† Our figures added for sake of comparison

TABLE 3.—HOSPITAL INCIDENCE OF VALVULAR HEART DISEASE, RHEUMATIC ARTHRITIS AND CHOREA.

(In Central Piedmont and Tidewater, Virginia.)

June 1, 1926, to June 1, 1932.	University Hospital, University, Va.		Hosp. of St. Vincent de Paul, Norfolk, Va.	
Total admissions	40,536		26,455	
Total rheumatic fever	No. cases, 200	Adm. rate %, 0 48	No. cases, 41	Adm. rate %, 0 15
Incidence major manifestations.	No. cases.	Per cent.	No. cases.	Per cent.
Valvular heart disease	138	69	22	53
Rheumatic arthritis	158	79	14	34
Chorea	34	17	5	12

ation is well supported by a rheumatic fever incidence in the piedmont section of Virginia of over 3 times that in tidewater Virginia (Table 3). Notable variations within this state itself thus occur, a situation almost certainly present in other sections, witness Los Angeles (rate 0.44 per cent) and San Francisco (rate 3.15 per cent) (Table 2). It cannot be assumed, therefore, that a given frequency

figure for one locality necessarily applies to another of approximately the same latitude though perhaps only 200 miles distant. However, as regards the admission rates listed for other hospitals, any exact comparison is impossible, since it is doubtful whether or not cases of valvular heart disease of rheumatic origin have been included under the heading of rheumatic fever (Table 2). At least, as far as Boston is concerned, rheumatic heart disease has been said to be twice as frequent as in this section of Virginia.[13]

In our series, patients were distributed according to race and sex as noted in Table 4. The figures obtained are in harmony with the observations of other investigators. The slight but definite trend to a higher incidence in the female is a commonly expressed, though unexplained, feature of the disease. The proportion of white to colored patients of 6.7 to 1 is a ratio which becomes 1.7 to 1 when corrected for the number of white to colored (4 to 10) admissions at this hospital. These figures would seem to indicate that rheumatic fever is decidedly less common in the negro than in the white, an observation previously noted by Longcope, who did not, however, give the ratio of white to colored admissions for Johns Hopkins. This contention is further supported by 3 rheumatic heart disease studies[14, 15, 16] in 2 southern states, although here again the assumption is not warranted that rheumatic heart disease necessarily represents a fair index of racial susceptibility to rheumatic fever. Even so, the inference is decidedly stronger than the single contrary contention of Atwater,[17] who has implied a high negro susceptibility on the basis of mortality statistics for acute rheumatic fever.

TABLE 4.—RACE AND SEX INCIDENCE IN 200 CASES OF RHEUMATIC DISEASE.

(From Central Piedmont Virginia; University Hospital, University, Va.)

	Males.	Females.	Totals.
White	85	89	174
Colored	11	15	26
Totals	96	104	200

NOTE.—White to colored ratio 1.7 to 1 when corrected for hospital admission frequency.

(From Medical Clinic, Johns Hopkins Hospital: Longcope.)

White	59	55	114
Colored	14	14	28
Totals	73	69	142

As already stated, each of the patients included in this study presented evidences of rheumatic arthritis, heart disease of rheumatic origin, or chorea at the time of observation or previously. An analysis of arthritic manifestations in the 200 cases is recorded in Table 5. The percentage of joint involvement as observed for this portion of Virginia would appear to be considerably higher than that noted by Longcope[11] for Baltimore and vicinity.

TABLE 5.—JOINT MANIFESTATIONS IN 200 CASES OF RHEUMATIC FEVER.

(From Central Piedmont Virginia.)

Arthritis.	No. cases.	Percentage (of all cases).
Arthritis, total	158	79.0
Arthritis, at time of admission	81	40.5
Initial attack	50	25.0
Recurrent attack	31	15.5
Arthritis, history only	77	38.5
Single attack	47	23.5
Recurrent attack	30	15.0
Total, single attacks	61	30.5
Rheumatic disease, no evidence of arthritis	42	21.0

In our 158 patients presenting evidence of arthritis, pain on joint motion was by far the most common symptom, although varying markedly in severity and often unaccompanied by appreciable swelling. The duration of joint symptoms in a single attack seldom exceeded 10 days except in prominent instances although recurrent attacks were noted in a relatively large number of cases. In only 3 persons were symptoms confined to a single joint. Forty-two patients were included in this series of 200 cases despite the fact that there were obtained no evidences from history or examination of past or present attacks of rheumatic arthritis. Of these, valvular heart disease was observed in 31 instances; in the remaining 11, Sydenham's chorea.

The occurrence of the several types of valvular heart disease observed in the 200 patients under consideration is described in Table 6. The high percentages derived attest the danger of serious cardiac involvement in the rheumatic disease of this section. Longcope[11] has noted a similarly high incidence of cardiac manifestations for the region of Baltimore and vicinity, and is of the opinion that for that locality, heart disease may be considered the chief form of the disease.

TABLE 6.—INVOLVEMENT OF THE HEART VALVES IN 200 CASES OF RHEUMATIC DISEASE.

(From Central Piedmont Virginia.)

Classification.	No. cases.	Percentage.
Valvular heart disease	138	69.0
Mitral stenosis and insufficiency alone	81	40.5
Aortic disease alone	18	9.0
Pure aortic regurgitation	14	7.0
Aortic regurgitation and stenosis	4	2.0
Mitral and aortic disease	39	19.5
Total mitral disease	120	60.0
Total aortic disease	57	28.5

Active rheumatic carditis was thought to be present at the time of observation in 106 cases, 54 of these falling in the group listed in Table 6, and 52 instances in which valvular disease of the heart could not be demonstrated. The criteria employed in a determina-

tion of activity for each case were these clinical and electrocardiographic evidences currently accepted as significant.

Sydenham's chorea had occurred or was observed in 34 of the 200 cases in this series (17 per cent). Of these 18 were associated with typical rheumatic fever, 5 with valvular heart disease, and in 11 cases chorea occurred alone.

Comment. The influence of some unknown factor in climate upon the incidence and course of rheumatic fever seems to have been satisfactorily established. Likewise, it would appear that the several manifestations of the disease vary in occurrence and severity for different localities. For example, Longcope has indicated that the cardiac syndrome commonly over-shadows the arthritic manifestations of the disease in Baltimore. Our own experience is essentially the same. Arthritis either by history or observation was recorded in 79 per cent of our patients (Table 5) (77 per cent, Longcope). Further, a low incidence of arthritis but a relatively high incidence of heart disease is seen in the figures for tidewater Virginia (Table 3). Here the recorded incidence of arthritis is definitely less than that either in piedmont Virginia or Baltimore, but the heart disease frequency remains comparatively high. An apparently low incidence of rheumatic arthritis therefore need not mean an equally low frequency of rheumatic heart disease. The best indication of the comparative frequency of rheumatic heart disease in piedmont and tidewater Virginia will be afforded by a careful survey of the school children of these two sections. Such a study is now in progress.

Summary. Two hundred instances of rheumatic disease, observed during a 6-year period at the University of Virginia Hospital, have been studied in an effort to determine the approximate incidence of the disease as a whole and to note particularly the relative occurrence of its various manifestations.

It would appear that rheumatic fever is of frequent occurrence in central piedmont Virginia, where it is 3 times as common as in the tidewater section of the same state. The arthritic forms of the disease, although mild and of such short duration as to suggest that they may at times escape detection, are relatively frequent and tend to recur in a fairly high percentage of cases. Serious and permanent damage to the heart is evidenced in a surprisingly large number of persons with rheumatic fever.

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A HEMORRHAGIC ERUPTION OF THE MOUTH AND THROAT IN THE RHEUMATIC STATE.

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Since the publication of Libman's classification of the endocarditides in 1923, the occurrence of petechiæ, especially those with white centers, has been associated with subacute or acute bacterial endocarditis. Libman[1] stated that petechiæ are found rarely in rheumatic fever and only as part of purpuric eruptions. Another lesion, however, heretofore undescribed, occurs frequently in the oral and pharyngeal mucous membranes in cases of chronic rheumatic endocarditis. It is a recurrent eruption, and has no diagnostic or prognostic significance in relation to the development of subacute bacterial endocarditis. While its appearance is not strictly limited to chronic rheumatic endocarditis, it is during the course of this infection that we have observed it most often during the past five years. Because the lesion is essentially one of the mucous membranes of the mouth and throat, and because it is unrelated to the presence of bacterial endocarditis or purpura, we regard it as a non-embolic hemorrhagic enanthem.

The eruption is seen in the mucous membranes of the cheeks, soft palate, sublingual region, fauces, uvula, the tip and borders of the tongue, and the tonsils. By far the most frequent site is the buccal mucosa, especially anterior and inferior to the opening of Stensen's duct. It consists of a circular, unelevated, deep red spot, varying in size from a pin point to 2 mm. in diameter. It may be present

alone or in groups of two or more. More rarely, one sees a shower of myriad pin points or a mosaic of larger spots distributed over the entire surface of the uvula or soft palate. In the buccal mucous membranes, pin point or slightly larger spots, occurring singly or in groups are the most frequent. Their color is usually the crimson of a fresh hemorrhage, but they may assume a darker, bluish hue. White centers have never been observed. The spots disappear or fade considerably after 24 hours. They are then very often promptly replaced by a new crop at the same site or elsewhere. Diffuse eruptions on the uvula or soft palate may persist for 2 weeks or more.

The comparative frequency of this lesion in patients with rheumatic infection and in apparently non-rheumatic subjects has been studied. Although it is seen rarely in the latter group, it is in chronic rheumatic heart disease, where rheumatic infection is recurrently or continuously active, that the enanthem makes its most frequent and repeated appearance. In a recently studied group of 19 cases of rheumatic valvular disease of the mitral and aortic valves, examined at biweekly intervals for 4 months, hemorrhagic spots were found in 9 cases at the initial examination and in a total of 13 cases during the period of study. Of 29 cases without rheumatic valvular disease, chosen at random for control, spots were found in only 1 case. Further observation on unselected cases revealed that the spots occur frequently during the course of a group of infections generally considered as indicating the presence of the rheumatic state. These include especially acute rheumatic fever, rheumatoid arthritis and erythema nodosum. It has been seen also in acute follicular tonsillitis and other acute upper respiratory infections, including otitis media. Other significant associations have been subacute bacterial endocarditis and congenital heart disease with unexplained fever, and cases of transient arthralgia and myalgia. The conditions in which the enanthem was seen unaccompanied by any evidence of rheumatic infection were malnutrition, diabetes mellitus, chronic vascular nephritis and mumps. Infrequently it has been found in apparently healthy children, and once in a case of idiopathic epistaxis in a healthy adolescent boy. Petényi[2] has described a similar constellation of hemorrhagic spots as a prodromal sign of measles before the appearance of Koplik spots.

The histologic features of the lesion are shown in Figs. 1 and 2. The specimen is one of buccal mucosa containing a spot. It was removed during an exacerbation of acute carditis in a male patient, aged 29, who had had chronic rheumatic mitral and aortic endocarditis for 10 years. In Fig. 1 there is a circumscribed area of hemorrhage which corresponds to the clinically observed lesion. It lies in the edematous squamous layer of epithelium. In all the sections examined there is increased vascularity of the epithelial and subepithelial layers. Fig. 2 illustrates the changes in the bloodvessels.

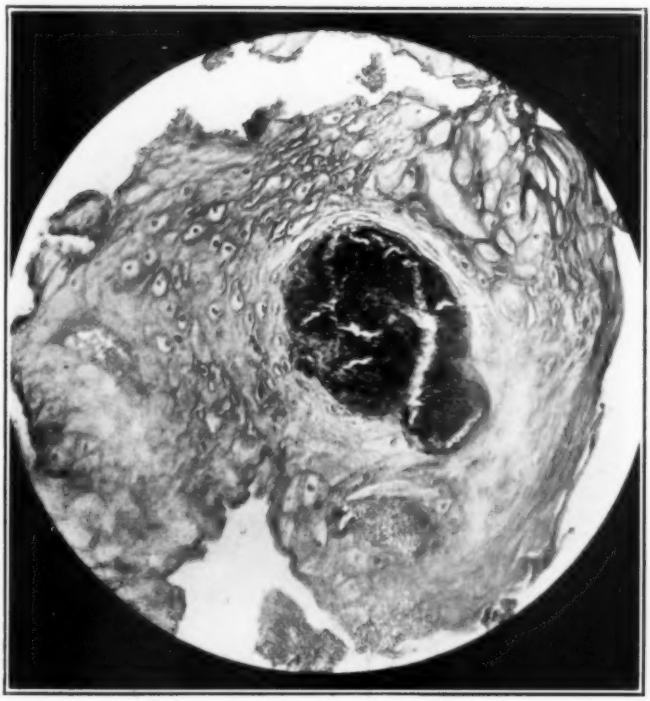

FIG. 1.—A hemorrhagic spot in buccal mucosa in a case of chronic rheumatic aortic and mitral endocarditis during an exacerbation of acute carditis.

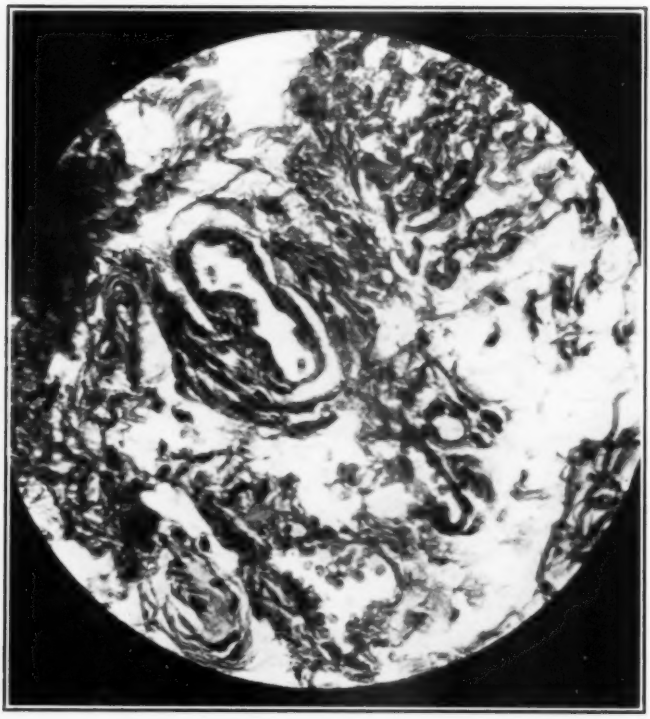

FIG. 2.—Vascular lesion in subepithelial tissue in vicinity of hemorrhage shown in FIG. 1.

These are thickening of the media and intima, endothelial proliferation and, in many vessels, a shelflike protrusion of the hyperplastic intima into the lumen. (Pathologic study by Dr. A. A. Eisenberg.)

Discussion. The nature of the diseases with which the above described enanthem most frequently is associated and the setting in which it appears, lead us to suspect that it is closely related to infections of the rheumatic type. Transient bacterial infections without clinical manifestations are now known to occur, and have been detected by chance positive blood cultures, positive skin tests with streptococcal filtrates and serologic reactions. The great frequency with which the lesion has been observed in chronic rheumatic heart disease in particular, and its occurrence in other conditions included under the generic term, the rheumatic state, further suggest that the spots may indicate repeated occult infections. In patients with chronic rheumatic heart disease, the relationship of the spots to upper respiratory infection and climatic conditions links them more closely to the rheumatic state. The enanthem is strikingly more frequent during the early spring and winter months when respiratory infections and acute exacerbations of carditis are endemic. With the advent of hot dry weather, the incidence of spots is relatively small. However, no constant relationship between their frequency and the activity of rheumatic infection, as indicated by the generally accepted criteria, such as fever, leukocytosis, sedimentation rate, joint pains, prolonged *P–R* intervals, etc., has been established.

The pathologic changes in the bloodvessels in the vicinity of the lesion are not distinctively rheumatic. Neither cellular infiltration nor fibrosis is present. Nevertheless, the arterioles present features which cannot be considered normal. It should be recalled in this connection that Klotz,[3] Pappenheimer and von Glahn,[4,5,6,7] and others have described the arterial lesions of rheumatic fever in other locations. Fraser[8] has described characteristic rheumatic lesions in the tissues of the pharynx and in the faucial and lingual tonsils.

The absence of specific rheumatic lesions and the occurrence of the enanthem in patients who have no other evidence of rheumatic infection lead us to defer a final evaluation of its significance until the concept of the rheumatic state has been further elaborated.

Conclusions. 1. An enanthem consisting of an eruption of hemorrhagic spots, was observed in the mucous membranes of the mouth and throat of patients with rheumatic heart disease.

2. It was also noted in other diseases included in the concept of the rheumatic state, and in relatively few patients in whom there was no apparent rheumatic infection.

3. It has been seen more frequently during the course of rheumatic heart disease than in any other condition and the seasonal peak of its frequency in this disease coincides with that of acute upper respiratory infections and carditis.

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THE NEURALGIAS OF THE HEAD AND FACE.*

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Trigeminal Neuralgia. The most common neuralgia of the face occurs in the distribution of one or more branches of the trigeminal nerve. Because of the characteristic type of pain, often described as stabbing, lancinating, knifelike and momentary, which follows the course of the anatomical distribution of the 5th nerve and is induced by cold currents of air, lightly touching the face or by movements of the lips or jaw, it is readily diagnosed and correctly treated, either temporarily by alcoholic injection of the appropriate branch of the 5th nerve, or permanently by intracranial section of the sensory root of this nerve somewhere central to the Gasserian ganglion. This pain is often erroneously ascribed to sinusitis and diseased teeth for which prolonged treatment is often instituted without the slightest effect. Spontaneous remissions for weeks or months occur for no apparent reason. Following a coryza or acute sinusitis the tic may reappear, frequently more severe and of longer duration than in former attacks.

Atypical Facial Neuralgia. Occasionally associated with this trigeminal tic douloureux is the so-called atypical facial neuralgia which is believed to be of sympathetic origin. It has been confused with Sluder's neuralgia, but cocainization or injection of the sphenopalatine ganglion gives no amelioration of the pain. The pain of an atypical facial neuralgia is more constant, lasting for hours or days, varying in intensity and developing exacerbations of intense sharp pain. This neuralgia is described as a deeply seated, burning, throbbing, aching pain in the temporal, zygomatic, maxillary and nasal regions, behind the eye, in the nose, the cheek, the gums, and at times just behind the ear.

Flothow,[1] Mixter and White[2] were the first to offer relief to

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patients suffering from this atypical neuralgia when they ablated the sympathetic chain in the region of the first, second and third thoracic ganglia. Recently Fay[3] has shown that the network of sympathetic fibers in the region of the carotid bifurcation plays a rôle in the causation of this neuralgia, which may explain the partial relief at times obtained after ablation of the upper cervical sympathetic ganglion. Apparently these sympathetic painful impulses may be conveyed to the brain not only by the cervicothoracic chain into the spinal cord and then cephalad, but also from the carotid plexus to the vagus and then to the brain. An illustrative case may elucidate the symptoms of both trigeminal tic douloureux and atypical facial neuralgia.

Case 1.—Mrs. M. C., aged 48, entered Lane Hospital in September, 1929, complaining of facial neuralgia for 20 years. At first there were small flashes of sharp pain in the right upper incisor tooth which had been crowned. She endured these transient attacks for 3 years when the crown was removed and the nerve killed. This treatment gave freedom from pain for 2 years. Then a stabbing pain appeared in the right temple, cheek and upper jaw as "terrible electric shocks." It seemed to start in the upper lip and cheek and was induced by touching these parts or the inside of the cheek, nose or gum, or by drinking cold water. Occasionally the lancinating pain spread to the lower jaw or to the forehead. She also complained of a deep-seated pain in the right zygomatic region in or behind the eye, and deep in the frontotemporal region. This aching pain at times was independent of the ticlike pain. Teeth were removed but she remained incorrectly diagnosed for 15 years. Attempts were then made to give relief by peripheral alcoholic injections.

In September, 1929, the sensory root of the 5th nerve was completely avulsed by Dr. Emile Holman, producing anesthesia over the whole distribution of the 5th nerve and completely curing the ticlike "electric shocks."

In July, 1931, she returned because of right occipital headache and burning of the right side of her cheek, tongue and lips, these areas having the sensation of being scalded. Lightly rubbing the right eye caused a severe burning, drawing pain. There was a tingling sensation of the right face and the same severe aching pain in the zygomatic and right maxillary region.

Injection of the sphenopalatine ganglion with novocain had no effect, but a novocain block of the right sympathetic chain at C_7, T_1 and T_2 relieved these complaints nor could they be induced during the period of sympathetic block by rubbing the eye. An alcoholic injection of the sympathetic chain was then made at the level of C_7, T_1 and T_2. A severe neuralgia of the arm and upper chest persisted for 6 weeks. Since the alcoholic injection ($1\frac{1}{2}$ years) she had been free of her occipital headache. The burning in the lips, temple, tongue and cheek disappeared but the tongue has a mild feeling of being "scalded." Neither rubbing the eye nor placing cold objects on the face causes the burning sensation. She no longer feels the tingling in the face, and the aching pain in the zygomatic and maxillary areas has disappeared.

There have been 5 patients with this combination of trifacial tic douloureux and atypical facial neuralgia. The tic pains were relieved by interruption of the 5th nerve. Three were relieved of the atypical neuralgia by alcoholic interruption of the upper thor-

acic sympathetic chain, but in 2 no amelioration of symptoms was secured from the sympathetic block. One of the latter, who also recently had the sympathetics in the region of the carotid bifurcation removed as well as the superior cervical ganglion, was only partially relieved of her symptoms.

Sphenopalatine and Vidian Neuralgia. The symptoms of atypical facial neuralgia are similar to those of sphenopalatine (Sluder's) and vidian neuralgia and it may be that a common factor will be found as the cause of these neuralgias. In some of the atypical neuralgias cocainization or injection of the sphenopalatine ganglion has brought no relief. Nor has washing of the sinuses been of any help. Vail[4] feels that sphenopalatine and vidian neuralgia are the same, since the irritation in the vidian nerve from a sphenoid inflammation could extend forward to the sphenopalatine ganglion and its terminal orbital, nasal and palatine branches as well as backward to the geniculate ganglion of the 7th nerve through the great superficial petrosal nerve and through the great deep petrosal nerve to the internal carotid sympathetic network.

Sluder's neuralgia is described as pain in the root of the nose, in and about the eye, in the upper jaw and teeth extending beneath the zygoma to the ear, and frequently to the occiput, neck, shoulder and arm.

Vidian neuralgia is characterized by pain in the nose, face, eye, ear, head, neck and shoulder which comes in severe attacks and which has been relieved, as have cases of sphenopalatine neuralgia, by treating disease in the sphenoid sinus.

Perhaps, as Vail believes, too little attention has been given to sphenoiditis as the cause of these neuralgias. Certainly with syndromes (atypical facial neuralgia, sphenopalatine neuralgia and vidian neuralgia) so similar, one should thoroughly investigate the sphenoid sinus before attempting to bring relief by other means.

Migraine. Although attacks of migraine may be initiated by fatigue, menstruation, food idiosyncrasy and other exciting causes, the underlying neurologic mechanism which produces the hemicrania and such other disturbances as hemianopsia, paresthesias, ophthalmoplegia, unilateral pallor or flushing, lacrimation and nasal congestion would indicate involvement of the sympathetic nervous system. Many "remedies" have been tried, but none seems to bring relief in every case. Recently Dandy[5] reported complete relief in 2 patients for $2\frac{1}{2}$ and $6\frac{1}{2}$ months after removal of the inferior cervical and first thoracic sympathetic ganglia. Penfield[6] felt that sympathectomy in the cervical region, which not only removed the chain but the plexus on the carotid and vertebral arteries, was insufficient. From experimental work with his associate, Chorobski,[7] and from the work of Davis and Pollock,[8] he concluded that referred pain in the head, such as in migraine, was of sympathetic origin from fibers accompanying the fibers of the trigeminal nerve, joining them

central to the Gasserian ganglion and following the ophthalmic branch of this nerve in particular. In 1 case of migraine Penfield secured relief for 3 years after complete cranial sympathectomy including intracranial division of the medial or ophthalmic group of posterior root fibers of the 5th nerve.

In 4 patients seen during their attacks of migraine we have injected the stellate and first and second thoracic sympathetic ganglia with novocain. One patient was not relieved; in another the headache stopped with the introduction of the needles before injection and the other 2 had their attacks stopped for the duration of the novocain block. One of the latter has reported 80 to 90 per cent improvement in the subsequent attacks although she had only a novocain injection.

Eighth Nerve Neuralgia (Ménière's Disease). A cure for true Ménière's disease by intracranial division of the affected 8th nerve was reported by Dandy[9] in 1928. At that time 9 cases had been relieved from 3 months to 3½ years. A subsequent article[10] reported 30 cases (some having been observed 6 years after operation) in whom there had not been a single attack resembling Ménière's disease subsequent to operation. Coleman and Lyerly[11] and a recent case of ours have substantiated the results of Dandy.

That Ménière's disease is a true neuralgia of the 8th nerve is suggested by the story of a patient "who is perfectly well in every respect, suddenly, without warning and without apparent cause, is seized with a terrific dizzy spell, lasting for several minutes, sometimes hours or even days. The dizzy spell passes off and the patient again is perfectly normal until at a later time a similar attack develops, and again without warning. From that time on life is a succession of just such attacks. Associated with the attacks there is usually vomiting and frequently nausea. Always there is tinnitus and subtotal deafness in one and the same ear." Dandy also describes pseudo-Ménière's disease where the attacks are exactly like those of Ménière's disease but there is never unilateral deafness. Only in true Ménière's disease has section of an already impaired nerve given complete and permanent relief.

So-called Geniculate Ganglion Neuralgia. Ramsay Hunt's neuralgia is of rare occurrence. From observation of patients with Bell's palsy and herpetic vesicles on and in the ear Ramsay Hunt described a neuralgia or otalgia characterized by sharply localized pain in the ear and mastoid region which he felt was due to irritation of the sensory filaments of the 7th nerve, that is, a neuralgia of the nervus intermedius or nerve of Wrisberg and the geniculate ganglion. Clark and Taylor[12] in 1909 reported the only case of a true tic douloureux of the sensory filaments of the facial nerve cured by physiologic extirpation of the geniculate ganglion. Taylor cut the 7th, the pars intermedia and the upper fasciculus of the 8th nerves intracranially. His patient was a woman, aged 28, who for 2 years

suffered from paroxysmal intermittent pain in front of the left ear and in the depths of the ear on the anterior wall of the external meatus. At times there was a moderate degree of neuralgic pain in all three distributions of the 5th nerve and also in the occipital region. As all eye, ear, throat and general physical examinations were negative, the conclusion arrived at by a number of neurolgists was that the lesion was a true tic douloureux of the geniculate system of the facial nerve, and that cutting the nerve of Wrisberg or pars intermedia should cure the condition. Following operation "on the twelfth day the patient sat up in a chair 45 minutes. That evening for 2 hours she suffered severe pain in the left ear, which closely resembled the pains before operation. With that single exception she has never for a moment had anything resembling the old pain." Six years later she was seen by Dr. George Crile who reported that she had remained free of pain.

Following the report of this case of a tic douloureux confined to the ear, a controversy appeared in the literature with Mills[13] and Kidd[14] opposing the teaching that the geniculate ganglion in man sends sensory fibers to the skin of the external ear and external auditory meatus. Mills went so far as to suggest, apparently correctly, that it was the decompression resulting from the operation rather than the section of the nerve that cured Taylor's patient. Kidd agreed that there were cases of herpes auris with complete homolateral facial palsy that corresponded closely in the distribution of the herpetic vesicles with Hunt's "zoster zone of the geniculate" but Mills felt that even these cases could be best explained on the supposition of an involvement of ganglia other than the geniculate.

Clark's and Taylor's report remained in the literature as the only case of true tic douloureux of the ear (geniculate neuralgia) that had been operated upon until our recent report[15] of a similar case which was cured by cutting the 9th nerve intracranially and which was termed typanic plexus neuralgia.

Tympanic (Jacobson's) Plexus Neuralgia. In the fall of 1932 a patient was studied in the various departments of our clinic because of severe left aural pain which was paroxysmal in character and seemed to be situated deep in the external auditory meatus. Her story was practically that of Clark's and Taylor's patient so that all concurred in a diagnosis of Hunt's or geniculate neuralgia or tic douloureux of the 7th nerve. Her history and operative findings are briefly summarized.

Miss R. S., aged 31, American, telephone operator, was referred to the Stanford Clinic by Dr. D. Carson in October, 1932. In 1921 a painful left concha caused her to dispense with the left ear phone for a time. Several months (spring 1932) before the onset of her complaint she had a sensation of drawing and discomfort in the left upper half of her face. Early in August the drawing sensation was quite extensive involving the cheek,

forehead and occipital region. A great pressure seemed to be on the bridge of the nose. At this time she had a coryza and an acute sinusitis. Two days later a sharp stabbing pain struck deeply in her ear, causing her to shriek and drop her work for 5 minutes. A number of paroxysms of stabbing pains appeared at irregular intervals throughout the day. They were all identical in type and location, coming without apparent cause as a momentary stab in the anterior wall of the left external auditory meatus and causing her to shriek and grab the side of her head and ear. These paroxysms continued daily. At times there was itching in the external meatus and a dull aching of the ear. A burning sensation of the left face continued for some time after an attack. Left occipital headaches were frequent. When seen in an attack she suddenly cried out, grabbed her left ear or put her little finger into the auditory canal and rocked back and forth in agony. There was no salivation during attacks.

Because there was swelling and injection of the posterior, superior wall of the external auditory canal which was tender but was not a trigger area for the paroxysms, efforts were made to eradicate any foci of infection. Roentgenograms showed evidence of maxillary and ethmoid disease. Antrotomy was done, the sphenoids and ethmoids were examined and washed. Teeth were extracted. The attacks of neuralgia continued and a fairly constant pain developed in the left face beneath the eye. The sphenopalatine canal was cocainized which relieved the pain in the ear and face for an hour. The sphenopalatine ganglion was injected with novocain and she was free from pain for 12 days. When it returned the ganglion was injected with alcohol but relief was secured for only 4 hours. Points of tenderness along the left cervical chain were obtained on pressure causing pain in the ear and dilatation of the left pupil but a novocain block of the left sympathetic chain at C_7, T_1 and T_2 did not stop the paroxysms, nor did cocainization of the tonsillar region and base of the tongue.

Trichlorethylene inhalations gave no relief. The tics were becoming more frequent and the patient was forced to stop work the latter part of November.

Roentgenograms of the mastoid regions showed a small double spot of increased density on the left which appeared like calcified débris or a tiny sequestrum, but Dr. R. R. Newell was unwilling to make a diagnosis of any mastoid inflammation from the roentgenograms. The skull and cervical spine were normal. Six weeks after the first examination of the ear the canal was slightly injected and when stroked with cotton showed a relative hyperesthesia. The tympanic membrane was of good color and position. The dull pain in the face continued. Hyperthermic baths increased the severity of the pains, galvanism gave no relief.

During the first week in December the paroxysms were coming every 1 to 3 minutes. Sedatives helped very little and the patient begged for relief. As it seemed a true tic douloureux of the geniculate ganglion and similar to the case of Clark and Taylor, operation was advised and permission given to section the 7th and 8th nerves if necessary in attempting to divide the pars intermedia of the seventh.

Operation was performed on December 10, 1932, under local anesthesia. Dandy's[16] unilateral cerebellar approach was made. The 8th, 9th and 10th nerves were easily identified and separated from each other. The 8th nerve was readily exposed and with the 7th was gently touched and moved. The patient stated she felt pain in her external auditory canal but that it was not the tic pain. The 9th nerve was touched which caused her to shriek and to exclaim that she had the tic pain. Four times the 7th and 8th nerves were gently moved and each time when questioned she stated she had a pain in the auditory canal. Four times the glossopharyngeal nerve was gently touched and each time she shrieked out from the stabbing

paroxysmal pain which was identical with the paroxysms she had had for 4 months. The glossopharyngeal nerve was then cut and the patient fell asleep on the operating table.

Over 11 months have elapsed since operation. Never has she felt any suggestion of her tic pain nor has the pain in the face and occipital region returned. Three weeks after operation she was back at work at the telephone exchange, a happy and calm individual.

The salivary secretions were accurately and simultaneously collected from the parotid and submaxillary glands in this patient and in 2 other patients in whom the 9th nerve had been sectioned intracranially. Contrary to the accepted teachings we[17] found that there was an immediate and marked diminution in the secretion of these glands on the side operated upon which, however, approached that of the normal side by the 3rd postoperative month. Collection of salivary secretions of other patients with facial palsy and normal or absent taste and still others, through the courtesy of the otolaryngological department, with avulsed chorda tympani just distal to the facial canal after a radical mastoidectomy, indicated[18] that the secretory fibers to the salivary glands came from the 7th and 9th nerves and that those from the 9th nerve apparently did not course through its tympanic branch but passed peripherally by its auricular anastomotic branch to the facial, in which nerve, by going cephalad, they entered the chorda tympani. From the chorda tympani the fibers to the parotid gland joined the auriculotemporal branch of the 5th, and those to the sublingual and submaxillary joined the lingual branch of the 5th.

Thus a typical so-called geniculate ganglion tic douloureux was cured by intracranial section of the glossopharyngeal nerve.[15] The operation was performed under local anesthesia with the expectation that the pars intermedia of the 7th nerve was at fault and its section contemplated. Fortunately with the patient awake she correctly indicated the nerve involved and insured the successful result.

Following this astonishing revelation that a so-called geniculate neuralgia was really a glossopharyngeal neuralgia it was evident that the tympanic or Jacobson's nerve branch of the glossopharyngeal must have been the only portion of the nerve involved, and one might call it a tic douloureux of Jacobson's nerve or tympanic nerve neuralgia. In Harris'[20] book several case histories are classified under geniculate neuralgia which might properly be placed with partial or tympanic plexus neuralgia of the 9th nerve.

The Neuralgias of the Glossopharyngeal Nerve. Two types of neuralgia of the 9th nerve have been described,[15] the partial or tympanic plexus tic douloureux and the complete glossopharyngeal tic douloureux.

The ordinary complete glossopharyngeal neuralgia has only recently been recognized and is still being confused with tic doulou-

reux of the 5th nerve, or else is diagnosed hysteria or psychoneurosis. These poor sufferers have their teeth and tonsils removed, their sinuses and ears treated and their 5th nerve injected or avulsed with no relief from the stabbing lancinating pain, which usually starts in the tonsillar region or base of the tongue and frequently radiates deeply into the ear. Eating, chewing, swallowing or talking or other movements of the tongue or pharynx induce the attacks and frequently a trigger zone is found in the tonsillar fossa or on the lateral side of the base of the tongue. Saliva drools from the mouth during attacks. Occasionally certain areas on the ear are sensitive and when touched may induce an attack. The mouth and pharynx appear normal and the diagnosis is dependent on the characteristic history and the fact that cocainization (10 per cent) of the tonsillar region and base of tongue will stop the attacks immediately. As reported recently in 3 cases,[19] permanent relief is secured by intracranial section of the 9th nerve, which produces no physical handicap, since the resulting unilateral numbness of the nasopharynx, from Eustachian tube to epiglottis, of the soft palate, posterior pharyngeal wall and tonsillar region, and the loss of taste and sensation over the unilateral posterior third of the tongue, are not noticeable to the patient except by clinical test.

When the patients with glossopharyngeal tic douloureux are operated upon under local anesthesia, their paroxysmal pains in the tonsillar region, the base of the tongue and deep in the ear are reproduced on moving or touching the 9th nerve. Fay[3] has recently described pain in these regions on faradic stimulation of the hypoglossal nerve. Also stimulation or traction on the vagal stump in another case gave direct reference of pain into the tongue, pharynx and ear, suggesting that the hypoglossal nerve carries pain fibers, which it receives extracranially directly from the vagus.

Whether this pain of vagal origin was similar or not to the paroxysmal type of pain that our 3 patients with complete glossopharyngeal neuralgia had is difficult to say. Our first patient with a trigger zone in the tonsillar fossa and a sensitive tragus, movement of which would induce pain, was operated upon under local anesthesia. The 9th nerve was close to the 10th and in freeing it from the upper fibers of the vagus the pulse slowed and subsequently, for a time, he had difficulty in swallowing large boluses of food and a slight weakness of the soft palate attributed to temporary injury to the 10th nerve; yet it was only when the 9th nerve was touched that his pain was reproduced. Likewise the case of tympanic plexus neuralgia experienced pain in the external auditory canal in the approximate region as that of the pain when the 7th and 8th nerves were moved; yet the reproduction of the tic pain occurred only when the 9th nerve was manipulated.

Fay[21] described 2 patients with malignant disease of the base of the tongue annoyed by dull aching pain deep in the ear. One patient

was not relieved by section of the trigeminus and glossopharyngeus intracranially but the other was relieved of the otalgia by peripheral section of the roots of the vagus. Vagal section gave anesthesia of the concha of the ear and a small area over the mastoid region.

Otalgia, according to Fay's observations, is of vagal origin. However, his patients suffering from malignant disease experienced "dull aching pain deep in the ear," whereas our patient and the one of Clark and Taylor suffered from true tic douloureux of the ear.

Summary. Of all the neuralgic pains in the head and face only those of paroxysmal nature can be classified as a true tic douloureux.

True tic douloureux of one, two or all branches of the 5th nerve is well known and is permanently cured by section of the nerve central to the Gasserian ganglion.

True tic douloureux of a branch (tympanic or Jacobson's nerve) of the 9th nerve has just been described. It has heretofore been considered as a geniculate ganglion neuralgia or tic douloureux of the sensory filaments of the 7th nerve.

True tic douloureux of all the branches of the 9th nerve (glossopharyngeal neuralgia) is being recognized more frequently with over 40 cases reported in the literature. Those in whom the nerve has been sectioned intracranially have been permanently cured.

True tic douloureux of the 8th nerve may be so considered since the paroxysmal character of Ménière's disease is similar to the tics of other nerves. Some 40 cases have remained cured after intracranial section of the 8th nerve.

All of the tics douloureux of the cranial nerves just mentioned, 5th, 8th, and 9th, have been permanently cured by intracranial division of the respective nerves.

Such complete success in treatment has not followed in the case of the other neuralgias of the head and face, such as the atypical or sympathetic facial neuralgia, sphenopalatine or Sluder's neuralgia, vidian neuralgia, migraine and otalgia with facial palsy (Hunt's or geniculate ganglion neuralgia).

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A SIMPLIFIED APPARATUS FOR DIRECT VENOUS PRESSURE DETERMINATION MODIFIED FROM MORITZ AND V. TABORA.

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In the office of practically every physician one may find a sphygmomanometer for ascertaining arterial pressure, but in very few offices, in fact in few institutions, is there to be found an apparatus for measurement of venous blood pressure. An accurate determination of this pressure is of almost as much value as that of arterial tension in diagnosis and treatment of cardiovascular disease. In the past, venous pressure was considered of significance only in the diagnosis of congestive heart failure. Recently, however, it has been recognized that venous pressure determinations have a differential diagnostic value in numerous other conditions. In our experience, this has been true in constrictive pericarditis, asthma, chronic pulmonary diseases, abdominal conditions associated with ascites, and obstruction to either vena cava by mediastinitis or tumor. These readings have also been of assistance in determining the necessity for venesection and the response to therapy in cases of congestive heart failure and in evaluating the results of surgery in constrictive pericarditis.

There are, in general, two methods by which venous pressure may be measured: direct and indirect. The indirect method depends upon the external pressure necessary to collapse a vein and, aside from numerous technical objections, necessitates equipment beyond financial reach of many physicians if accurate readings are to be obtained. The direct method is a direct measurement of the pres-

sure within a vein by means of a manometer connected with a needle or cannula introduced into the vessel.

Moritz and v. Tabora, in 1910, described an apparatus and technique for venous pressure determination from which the apparatus described below is modified. The original mechanism was complicated and not well suited for practical clinical use. We shall endeavor to describe an apparatus which every practitioner, no matter how limited his resources, should be able to assemble and use to advantage.

The materials used in the assembly are: a glass tube of even

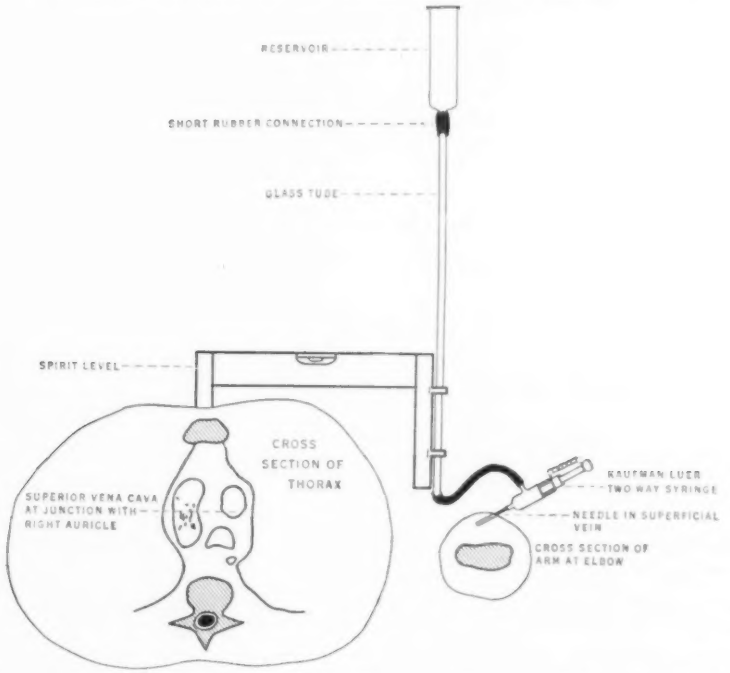

FIG. 1.—Diagram of apparatus in use. The reservoir on top is disconnected when flow into vein is established.

bore, about 35 cm. long (a pipette delivering 1 cc. is very satisfactory), the barrel of an ordinary 10- or 20-cc. syringe, a Kaufman-Luer side arm syringe, a 20-gauge needle of 1½ inch length, and 2 pieces of rubber tubing (14-F. catheter size), one about 30 cm. long and the other about 4 cm. long. The short piece of rubber tubing is used to connect the reservoir with the top of the glass tubing. The longer rubber piece connects the lower end of the glass tubing and the side arm of the Kaufman-Luer syringe. The needle is placed on the Kaufman-Luer syringe.

Before a venous pressure reading can be made on a patient, the

entire apparatus must be sterilized, which can easily be done in an ordinary sterilizer. The reservoir is filled with sterile physiologic saline solution and then the entire apparatus is filled by lowering the Kaufman-Luer syringe and pulling back its plunger to open the side arm. After precautions are taken to see that no air bubbles are present, the plunger of the two-way syringe is pushed in to the closed position. The apparatus is now ready for venipuncture.

After the patient has been at rest in the supine position, in bed or on a stretcher, for at least 15 minutes, the arm and forearm are extended by the side in supination so that any prominent superficial vein in the cubital fossa is approximately on a level with the right auricle. This, in the average patient, is in a plane about $2\frac{1}{2}$ inches dorsal to the angle of Louis or, roughly, on a level with the mid-axillary line. A tourniquet is placed on the upper arm to distend the selected vein. After the area to be punctured is prepared with iodin and alcohol, the needle is introduced well into the lumen of the vein. The plunger of the Kaufman-Luer syringe is now withdrawn, allowing the venous blood to enter the proximal $\frac{1}{3}$ of the syringe barrel. A free back flow of blood indicates that the needle is in the correct position. The tourniquet on the upper arm is now released and as an assistant holds the glass tube and the attached reservoir upright, the Kaufman-Luer syringe plunger is pulled back to open the side arm. The locking chain prevents complete removal of the plunger and serves to hold it steady while a reading is being made. The above maneuvers connect the vertical column of saline directly with the blood stream in the vein lumen. Within reasonable limits (below a pressure in the vein of 350 mm.) the fluid level in the reservoir will begin to fall slowly and the contents of the two-way syringe will begin to clear as the saline enters the vein. As soon as this has occurred the reservoir above is disconnected and put aside. The glass tube is now adjusted so that its lower end, the zero point, is on a level with the needle at its point of entrance into the vein, the tube being held always in a vertical position. The fluid level now falls until the pressure of the column of fluid equals the pressure within the vein.

At this point, in some patients, the height of the fluid column will fluctuate slightly due to changes in the intrathoracic pressure occasioned by the respiratory cycle. In other cases a wave timed with the pulse may be noted. Additional evidence that the fluid column has reached its lowest level is to lower the glass tube a short distance. If the pressure of the fluid column is equal to the venous pressure, the column will immediately rise as the tube is lowered. Conversely, raising the tube will cause the fluid column to drop. At this point, after allowing the column to come back to its original position of equilibrium, we always have the patient increase his intrathoracic pressure by forced efforts at expiration with his glottis closed—*i. e.*, the Valsalva experiment. This will cause a rise in the

height of the fluid column if the system is patent. The patient is now allowed to breathe as before and the column falls to its previous level. The height of the fluid column is now measured by means of a ruler or a steel tape. This measurement, with certain minor corrections to be described below, is the venous pressure. If one obtains a glass tube calibrated in millimeters, or a millimeter scale which may be attached to a plain glass tube, this bother of measuring with a ruler or steel tape is obviated.

Because of the necessarily small lumen of the needle and tubes used in these determinations, a factor of error is introduced by the capillarity. It therefore becomes necessary to make a slight correction

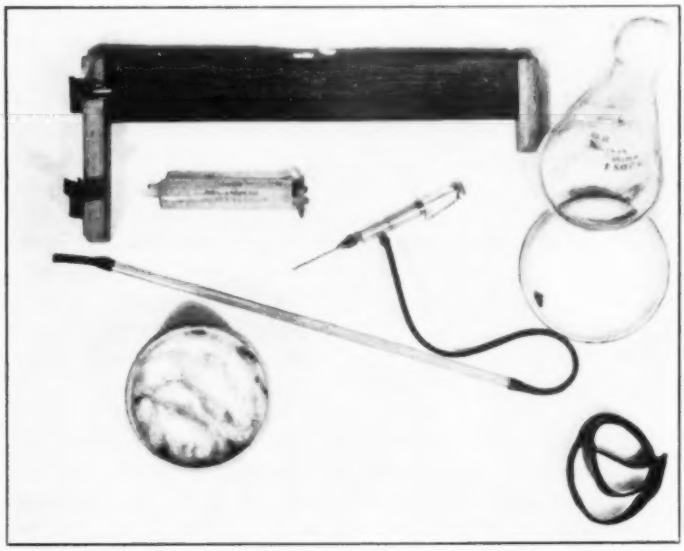

FIG. 2.—Material necessary for determination apparatus, spirit level, alcohol sponges, normal saline and a tourniquet.

in each reading. In order to determine this error due to capillarity, the apparatus is filled with saline as if in preparation for a venous-pressure reading and the needle point immersed in a receptacle containing normal saline. With the lower end of the upright glass tube at the level of the surface of the saline in the receptacle, the system is opened by pulling back the plunger of the two-way syringe. The column of fluid in the glass tube will fall, coming to a standstill somewhere above the zero point. The distance between the top of the fluid column and the zero point measured in mm. is the correction for capillarity and should be subtracted from all the readings made with this particular apparatus. It is most convenient, if a series of determinations on one or more subjects is being made, to employ the same apparatus or duplicates thereof. If, however,

this is impossible, it is most important to calibrate each apparatus for capillarity by the simple method described above.

When indicated, femoral vein readings may be readily and accurately made without any more risk to the patient than arm determinations. The optimal site for venipuncture is a point located at the proximal end of the femoral trigone, about 1 inch distal to the inguinal ligament and just mesial to the point of maximal pulsation of the artery. A tourniquet, of course, cannot be used and is not needed. The zero point of the glass tube is held in the plane of the midaxillary line, provided the patient is on a firm stretcher and not in a sagging bed. The technique is otherwise just as described for venipuncture in the arm veins. It might be helpful to state that we have found the femoral vein located from $\frac{1}{2}$ to $1\frac{1}{2}$ inches below the surface and often the needle must be introduced at an angle and to its fullest extent before the vein is reached.

During the course of repeated examinations, we soon discovered that it was difficult to place the arm in the correct position and that this frequently caused erroneous determinations and inaccurate technique. We were able to eliminate this by devising a very convenient, but not absolutely essential, addition to the assembled apparatus, namely, a spirit level with accurately measured uprights on each end. The uprights are so constructed that one is $2\frac{1}{2}$ inches longer than the other. The shorter upright is allowed to rest on the anterior chest wall at the level of the second costosternal junction (Louis' angle). The glass tube is held in place against the longer upright by two clamps which allow its ready release for cleaning and sterilization. With this addition to the apparatus the level of the vein to be punctured does not have to be taken so accurately into consideration, provided two conditions are fulfilled: first, that the patient be supine with the arm extended by the side; and second, that the lowermost or zero point of the glass tubing is at the lowest edge of the longest upright when the spirit level is horizontal. In different sized thoraces, adjustment should be made, by sliding the tube in the clamps, so that the zero point of the tube is opposite the midaxillary line, which is recognized as approximately the level of the superior vena cava.

In extremely decompensated patients, who are unable to assume the supine position, readings should be made with the arm raised and the zero point of the tube at the level of the second costochondral junction, the patient being as close to supine as possible.

Finally, we feel that we should stress the importance of the following small details: (1) Snugly fitting connections to guard against leakage. (2) Rubber tubing free of old blood clots and air bubbles, to insure an open system. (3) Clean, sharp needles for accurate and relatively painless venipuncture.

Venous pressure has even a wider range of normal than arterial pressure. In a series of 250 readings with this instrument, we have

found a normal range of from 60 to 120 mm. of saline, with the average normal varying from 80 to 110. Any reading above 140 or below 40 should be considered definitely pathologic. Because of the possibilities of error in these determinations, two or more readings, which check reasonably, should be taken on each case studied.

Summary. A simple and inexpensive apparatus for venous pressure determination by the direct method of Moritz and v. Tabora is described, together with the technique for its use.

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FACTS ON DISEASE OF THE CORONARY ARTERIES, BASED ON A SURVEY OF THE CLINICAL AND PATHOLOGIC RECORDS OF 762 CASES.*

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Valuable information concerning the morbidity and mortality from disease is obtained by analysis of clinical records and death certificates. But the facts are apparent only when the check of postmortem examination is critically applied. The increasing death rate from cardiovascular disorders has fired the imagination of the laity and aroused concern in the minds of those whose function it is to conserve the public health. Coronary artery disease, due perhaps in part to the dramatic features of acute obstruction and the frequency with which it terminates the careers of prominent citizens by sudden death, has stimulated an unusual amount of general interest. Certainly during the past two decades, disturbances in the coronary circulation have been subjected to intensive investigation, both in the laboratory and the clinic.

* Read before the American Climatological and Clinical Association, Washington, D. C., May 9, 1933.

In the files of the Presbyterian Hospital, during the period covered by the years 1910 to 1931 inclusive, 762 autopsy records were found in which affections of the coronary arteries were described. This particular span of years was chosen because the records kept during this time were adequately complete and sufficiently uniform for comparison. During this period, 126,445 patients were admitted to the hospital and 2877 autopsies were performed. Based upon a correlation of the clinical and pathologic data, a series of studies has been made. It is realized that this relatively small number of cases represents only a section of the population residing in a particular eastern American city and that, in view of such limitations with respect to the material, no general conclusions may be drawn. On the other hand the observations, both at the bedside and at the postmortem table, were made with reasonable care. And there is available in the records of the New York City Department of Health an ample background of general statistical information.* In this paper are presented some of the results of a statistical survey of our cases of coronary artery disease.† More detailed discussion of various aspects of this group of cases will appear in subsequent communications.

The Material Studied and the Manner of its Collection. It was apparent as the result of a preliminary study[1] that all cases showing pathologic changes in the coronary vessels were not indexed under coronary headings in the record files of the Department of Pathology. In the earlier years covered by the period under consideration, failure to file such data was due chiefly to lack of interest on the part of the person performing the autopsy; for adequate descriptions were given in the protocols. Even in later years, minor grades of atheroma, in the form of a few intimal plaques, were likewise not noted in the final anatomical diagnoses, perhaps because such changes were relatively common and were not regarded as significant. Indeed, at a given age, what character or extent of change in the arterial wall should be regarded as within the range of normal? At present, there exist no adequate criteria which make possible an answer to this query. In assembling our cases, the point of view was taken that the presence of any lesion signified a deviation from the normal and hence should be considered as pathologic.

In the endeavor to include, as nearly as possible, all of the cases in the autopsy files, each protocol indexed under the following headings was carefully examined: arteriosclerosis of the coronary arteries, thrombosis of a coronary artery, infarct of the myocardium,

* To Dr. Charles F. Bolduan, Director of Health Education of the New York City Health Department, we are grateful for placing at our disposal the records of this Department.

† We are indebted to Dr. Louis I. Dublin, Statistician and Vice-President of the Metropolitan Life Insurance Company, for helpful criticism with regard to the technique of statistical analysis; and to Mr. Goldstein of his Department, for tabulating the material.

aneurysm of the heart, fibrosis of the myocardium, embolism of a coronary artery, occlusion of the coronary arteries, syphilis of the aorta, stensosis of the orifice of a coronary artery, periarteritis nodosa, rheumatic coronary arteritis and generalized arteriosclerosis. Particularly under this last caption were found numerous cases showing the lesser grades of coronary sclerosis and not included in the diagnostic files as coronary disease.

For estimating the frequency with which the clinical diagnosis of coronary disease was made, only those records were included in which specific diagnostic mention was made of coronary lesions. Thus, cases filed merely as "syphilis of the aorta" or "generalized arteriosclerosis," without reference to coronary involvement, were discarded. In this group obviously there appear a number of fatal cases in which an autopsy was not performed, and others that did not die while under observation.

Discussion. *Etiologic Types.* It is apparent in Table 1, that arteriosclerosis was by far the most common lesion of the coronary arteries, having been found in 97.2 per cent of the cases. Infarction of the myocardium took place not infrequently in the absence of thrombosis. In 13 per cent of the infarcts, aneurysm of the ventricles developed. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the blood supply of the heart in 5.7 per cent of the total cases. In over one-quarter of the syphilitic group, the heart muscle was the seat of infarction. Coronary embolism was rare, occurring but six times in 2877 autopsies. Periarteritis nodosa involving the coronary vessels, was observed only 3 times and rheumatic coronary arteritis but twice.

Table 1.—Etiologic Types of Coronary Disease and Associated Pathologic States, in 762 Autopsies on Cases with Coronary Disease, 1910–1931.

Arteriosclerosis			742 (97.2%)
Slight	157		
Moderate	220		
Calcification, Stenosis or Occlusion	293		
Thrombosis	72		
Infarct of heart		93	
Aneurysm of heart		12	
Rupture of heart		3	
Syphilis of aorta			44 (5.7%)
Stenosis or occlusion of coronary orifice	44		
Infarct of heart		12	
Coronary embolism			6
Periarteritis nodosa (coronary periarteritis)			3
Rheumatic fever (coronary arteritis)			2
Coronary compression by amyloid deposits			1
Coronary compression by aortic aneurysm			1

It has been claimed, notably by Warthin,[2] that syphilis predisposes to the production of coronary sclerosis with its attendant pathology. The figures shown in Table 2 do not substantiate this

assertion, for in this group of cases syphilis was found at autopsy in but 13.4 per cent. This is approximately the incidence of syphilis in the general population of our hospital. As might be anticipated in a series in which 44 cases of luetic aortitis have been deliberately chosen for inclusion, it was in the younger patients that the incidence of syphilis was highest. The close agreement between the Wassermann reaction and the finding of syphilitic lesions at autopsy is noteworthy. In a series of 44 autopsies on cases of coronary disease, Klotz and Lloyd[3] were likewise unable to demonstrate a relation between syphilis and coronary sclerosis. They found evidences of syphilis in 11 per cent—a figure closely approaching ours. Syphilis, then, is present no more frequently in patients with coronary disease than in those without it.

TABLE 2.—INCIDENCE OF SYPHILIS, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910–1931.

	No. of cases.*				Per cent of total cases.			
	Total	25–44	45–64	65 and over	Total	25–44	45–64	65 and over
Total autopsies	746	133	408	194	100.0	100.0	100.0	100.0
Syphilis found	100	31	57	11	13.4	23.3	14.0	5.7
Total number tested by Wassermann	555	116	307	123	100.0	100.0	100.0	100.0
Positive Wassermann	82	24	53	4	14.8	20.7	17.3	3.3

* Age group "0–24" has been omitted because it comprised only 11 cases.

Incidence. For purposes of discussion, the interval covered by the years 1910 to 1931 has been divided into two time periods, namely, 1910 to 1919, and 1920 to 1931. In this way, the validity of any changes occurring during these 22 years is enhanced, in that the number of cases involved in the comparison is greater than if subdivision were made into annual periods.

TABLE 3.—COMPARISON BETWEEN CLINICAL AND AUTOPSY INCIDENCE OF CORONARY DIAGNOSES, BY TIME PERIODS, 1910–1931.

Period.	Total hospital admissions.	Clinical coronary diagnoses.	Total autopsies.	Autopsy coronary diagnoses.	Per cent clinical coronary diagnoses of total admissions.	Per cent autopsy coronary diagnoses of total autopsies.
1910–1919	40,682	7	1020	182	..	17.8
1920–1931	85,963	454	1857	564	.5	30.4
Total	126,645	461	2877	746	.4	25.9

During the second period, due to enlarged facilities in a new building, both the total number of hospital admissions and the total number of autopsies were greater than in the preceding 10 years (Table 3). As diagnosed clinically, the coronary cases comprised but a fraction of a per cent of the total number of hospital patients.

Yet 25.9 per cent of all cases which came to the autopsy table showed lesions of the coronary vessels. This figure corresponds closely to the incidence of significant degrees of coronary sclerosis in a series of 5060 consecutive, routine postmortem examinations at The Mayo Clinic, namely 28.2 per cent.[4] In Glasgow, in a series of 1000 consecutive autopsies, the incidence of coronary disease was even greater; 37.1 per cent of the cases showed a lesion, trifling or severe, by naked-eye observation.[5] The figures are strikingly high.

The Degree of Coronary Sclerosis by Age Groups. Affections of the coronaries due to those degenerative changes commonly called arteriosclerotic, were subdivided, quite arbitrarily, into four groups: (1) slight sclerosis, in which an occasional patch of intimal atheroma was present; (2) moderate sclerosis, in which such changes were more extensive; (3) calcification, stenosis or occlusion (the latter nonthrombotic); (4) thrombosis. The vascular lesions in the first group and in many of those in the second were of no functional importance in that they did not impair the nutrition of the heart muscle; and these two groups comprise 50 per cent of the total. Yet even the smallest plaque may assume vital significance if the integrity of the intima is impaired and thrombosis is initiated.

As might be expected, the lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developed with advancing years. Thrombosis, on the other hand, occurred with equal frequency during the age periods 25 to 44 and 45 to 64, and declined sharply after age 65 (Table 4).

TABLE 4.—DEGREE OF CORONARY SCLEROSIS, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910–1931.

	No. of cases.*				Per cent of total cases.			
	Total	25–44	45–64	65 and over	Total	25–44	45–64	65 and over
Total number rated	746	133	408	194	100.0	100.0	100.0	100.0
None†	4	2	2	..	.5	1.5	.5	
Slight	157	41	84	30	21.0	30.8	20.6	15.5
Moderate	220	44	124	49	29.5	33.1	30.4	25.3
Calcification, stenosis or occlusion	293	31	157	103	39.3	23.3	38.5	53.1
Thrombosis	72	15	41	12	9.7	11.3	10.0	6.2

* Age group "0–24" has been omitted because it comprised only 11 cases.

† Of these, 2 were cases showing rheumatic coronary arteritis; 1 was an instance of coronary compression by amyloid deposits; another, compression by an aortic aneurysm.

The Clinical Diagnosis. From 1910 to 1919, the diagnosis of coronary disease was made but 7 times in 40,682 hospital admissions. In 1919, J. B. Herrick published his second paper on thrombosis of the coronary arteries.[6] It is, perhaps, more than coincidental that during the year 1920, the diagnosis of coronary disease was

made 11 times. From then on, the trend of the incidence of coronary diagnosis was steadily upward, so that in 1931, 8 patients in every 1000 admitted were regarded as having impairment of the cardiac circulation (Fig. 1).

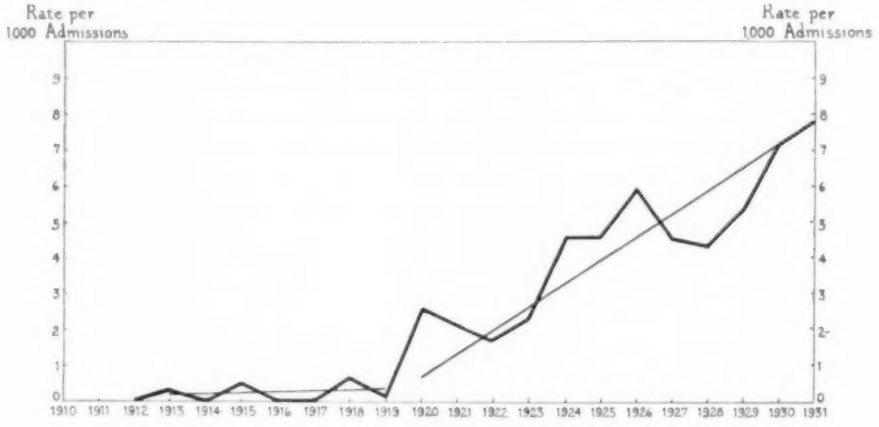

FIG. 1.—Clinical diagnosis of coronary disease per 1000 hospital admissions, 1910–1931.

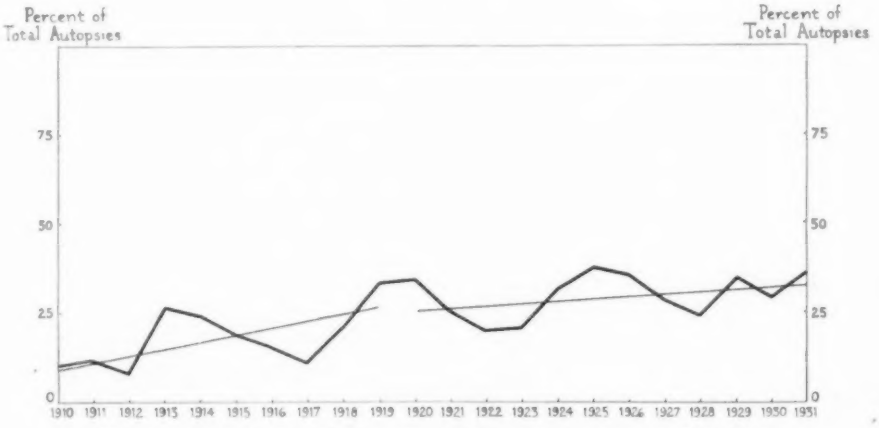

FIG. 2.—Per cent of total autopsies showing coronary disease, 1910–1931.

The Pathologic Diagnosis. On the basis of clinical diagnosis alone, it would appear that during the period under consideration there has been a considerable increase in the incidence of coronary disease. But the autopsy figures do not lend support to this idea (Fig. 2). To be sure, throughout the 22 years, the trend is gently but steadily upward. But the sharp discrepancy between the slope of this curve and the one shown in Fig. 1 is striking.

The Increasing Incidence of Coronary Disease. In this series of

autopsies, then, as time went on, the incidence of coronary disease actually increased. But the increase was not nearly so great in the proven cases as was indicated by the figures based on clinical diagnosis alone. There are several reasons in explanation of these facts:

1. In New York City, during the period 1910 to 1931, the general death rate has steadily fallen; the lowering of rate obtains at all ages. This decline in death rate has been due almost entirely to effective control of all of the important infectious diseases (Table 5).* Fewer people succumb to infections; but they escape only to die, at a riper age, of degenerative diseases.[7]

TABLE 5.—DEATH RATES PER 100,000 POPULATION, NEW YORK CITY, 1910, 1920 AND 1931.

	1910	1920	1931
Total death rate	1604	1289	1092
Pulmonary tuberculosis	181.64	108.47	61.64
Other tuberculosis	28.88	17.07	7.79
Pneumonias	219.83	176.96	130.39
Typhoid fever	11.66	2.41	1.09
Diphtheria	35.84	18.39	2.62
Scarlet fever	19.91	3.87	1.18
Cancer	77.53	93.53	117.57
Diabetes	16.05	18.91	27.09
Circulatory system diseases	220.08	267.34	331.27
Apoplexy	19.83	12.63	9.62
Bright's disease and nephritis	117.80	85.03	39.58

2. The population of the city during this same period consequently has "aged"—that is, there has been a progressive increase in the percentage of the population aged 35 and over (Table 6). Those in the later decades of life are more likely to suffer from the circulatory disorders associated with arteriosclerosis.

TABLE 6.—THE AGING POPULATION OF NEW YORK CITY. PERCENTAGE COMPOSITION, BY AGE GROUPS 1910, 1920 AND 1930.

	1910	1920	1930
Under 15	28.7	28.4	24.4
15 to 34	40.2	37.2	38.0
35 to 64	28.3	31.3	33.8
65 and over	2.84	3.11	3.83

3. There has been a change in fashion with regard to diagnostic terminology. The death rates from apoplexy, Bright's disease and nephritis, and senility have fallen off sharply. Cases formerly so designated have come to be included under the term "Circulatory System Diseases," and so have added to the numbers of the latter group[8] (see also Table 5).

4. Diagnosis is made with greater accuracy. As has been said on another occasion, physicians have become not only "heart-minded" but "coronary conscious."[1] Coronary thrombosis is now rarely called acute indigestion. It is a familiar fact that non-valvular heart disease—the "chronic myocarditis" of the older writers—

* The death rates for cancer and diabetes have risen; the reasons concerned are not pertinent to the present discussion.

is often associated with coronary sclerosis. Many of the milder, non-fatal and atypical forms of coronary disease are being recognized with increasing frequency.

In short, during the 22 years under consideration, there has been, in the autopsied cases, a slight but real and progressive increase in the incidence of affections of the coronary arteries. This may be explained chiefly by the decline of infectious diseases and the aging of the population. The much greater rise in the frequency of the clinical diagnosis of coronary disease is due in large measure to altered fashions in terminology and to sharpened clinical acumen. This state of affairs is not to be deplored or regarded as a matter of concern. Rather should it be a source of satisfaction that, due largely to effective control of infectious diseases, men may survive to an age when disorders incident to senescence carry them off. The prevention of vascular degeneration presents a problem as yet unsolved.

The Incidence According to Age and Sex. Coronary artery disease increased at all ages (Fig. 3). The increase is particularly noteworthy between the ages 25 and 44. There is a predominance of males (Fig. 4). In both sexes the number of cases in the later time period has become greater. In the women in this series, the incidence more than doubled.

The Incidence in Relation to Occupation. Those who emphasize the rôle of the strain of 20th century existence in causing coronary disease, call attention to the numbers of business executives with great responsibilities who succumb to its ravages. Our figures do not lend support to this point of view (Table 7). The largest percentage of coronary cases was found among foremen and skilled workers, *i. e.*, 44.2 per cent of the total autopsies in this occupational group showed coronary disease. The professional and executive group came second (39 per cent). Next in order of frequency came manual laborers, clerical workers, the semiprofessional and minor executive group, housewives, the retired or unemployed and, finally, the student group. (All of the students were under 25 years of age.) The differences are not great and, in this series at least, occupation has not seemed to play a highly selective part. The high incidence of coronary artery disease in a group of Jewish industrial workers has recently been pointed out,[9] but the observations were not controlled by postmortem examinations.

The Accuracy of Clinical Diagnosis. A study of Fig. 5 makes it clear that our clinical acuity has been sharpened. We have become more familiar with the protean manifestations of affections of the coronaries. The cases of slight sclerosis, in which an occasional plaque of intimal atheroma is the only evidence of pathologic change, will probably continue to escape detection when there is no associated functional impairment of the heart. Even where calcification and stenosis were present, the diagnosis was made

during life only in 16 per cent of the cases during the years 1920 to 1931. The figures for coronary thrombosis are especially striking. Thus, in the period 1910 to 1919, only 19 per cent of the cases were recognized at the bedside; in the period 1920 to 1931, 43 per cent were properly designated—an appreciable improvement in the

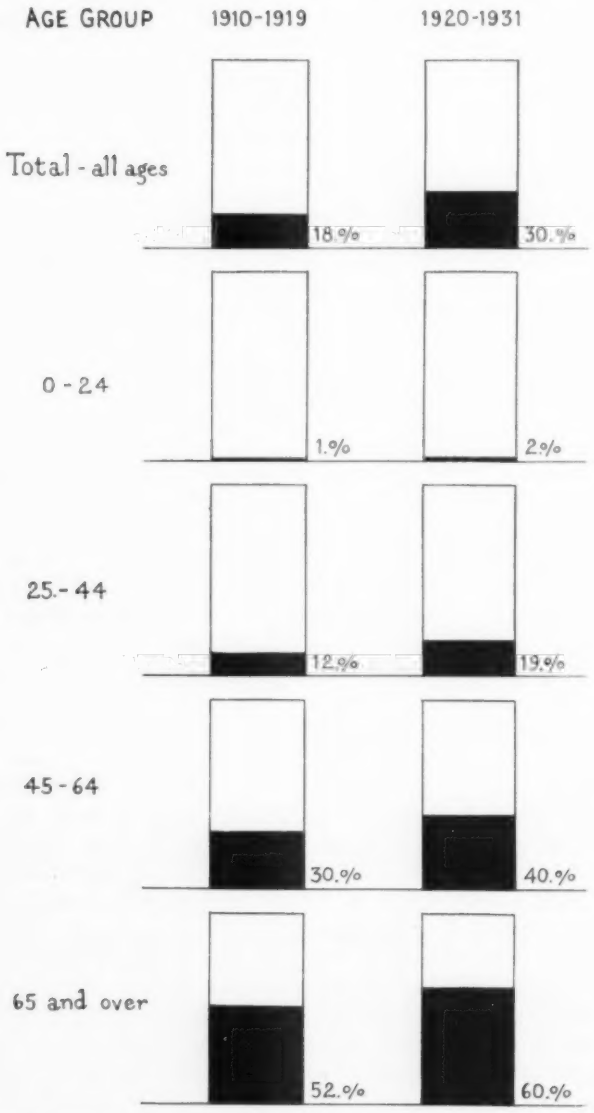

FIG. 3.—Per cent of total autopsies showing coronary disease, by age groups, 1910–1931, in two periods.

accuracy of diagnosis. That so many of these cases escaped detection was due in large part to the great number in which pain was slight or absent. The painless group presents a number of features of interest, and will be made the topic of a separate report.

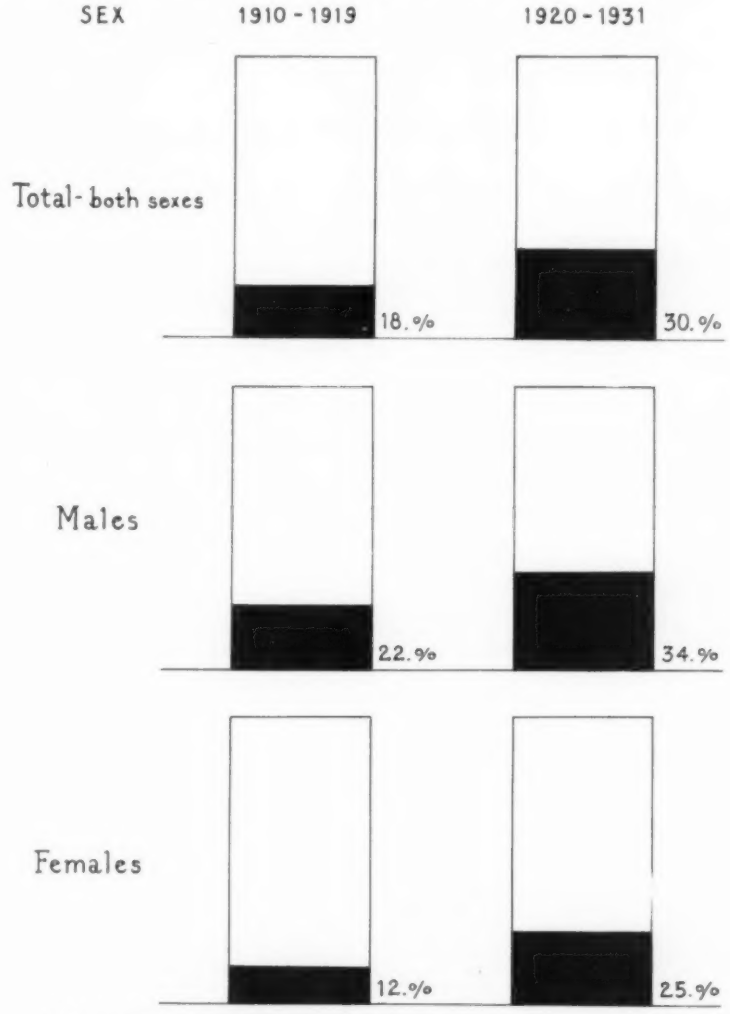

FIG. 4.—Per cent of total autopsies showing coronary disease, by sex, 1910–1931, in two periods.

If so many errors in diagnosis occur in a hospital where every necessary facility is at hand, how much more inaccurate must be the statements in death certificates filled out under less favorable circumstances, and unchecked by postmortem examinations.

TABLE 7.—INCIDENCE OF CORONARY DISEASE IN RELATION TO OCCUPATION IN 762 AUTOPSIES ON CASES WITH CORONARY DISEASE.

Occupational status.	1910–1919			1920–1931			1910–1931		
	Coronary cases.	Total autopsies.	Per cent coronary of total	Coronary cases.	Total autopsies.	Per cent coronary of total.	Coronary cases.	Total autopsies.	Per cent coronary of total.
Infants	...	158	0	...	125	0	...	283	0
Housewives	24	167	14.4	140	448	31.3	164	615	26.7
Students (under 25)	2	52	3.8	2	98	2.0	4	150	2.7
Manual laborers	71	317	22.4	197	537	36.7	268	854	31.4
Clerical workers	19	81	23.5	66	203	32.5	85	284	30.0
Foremen and skilled workers	23	64	36.0	50	101	50.0	73	165	44.2
Semiprofessionals and minor executives	8	45	17.8	30	89	33.7	38	134	28.4
Professionals and executives	17	49	34.7	49	120	40.8	66	169	39.0
No occupation (retired or unemployed)	14	54	26.0	30	113	26.6	44	167	26.4
Not stated	4	40	10.0	16	25	64.0	20	65	30.8
Total	182	1027	17.7	580	1859	31.2	762	2886	26.4

The Causes of Death. Although all of the patients in this series showed pathologic involvement of the coronary arteries, they did not all die of heart disease, nor was this necessarily the condition which induced them to enter the hospital. In the interest of clear-

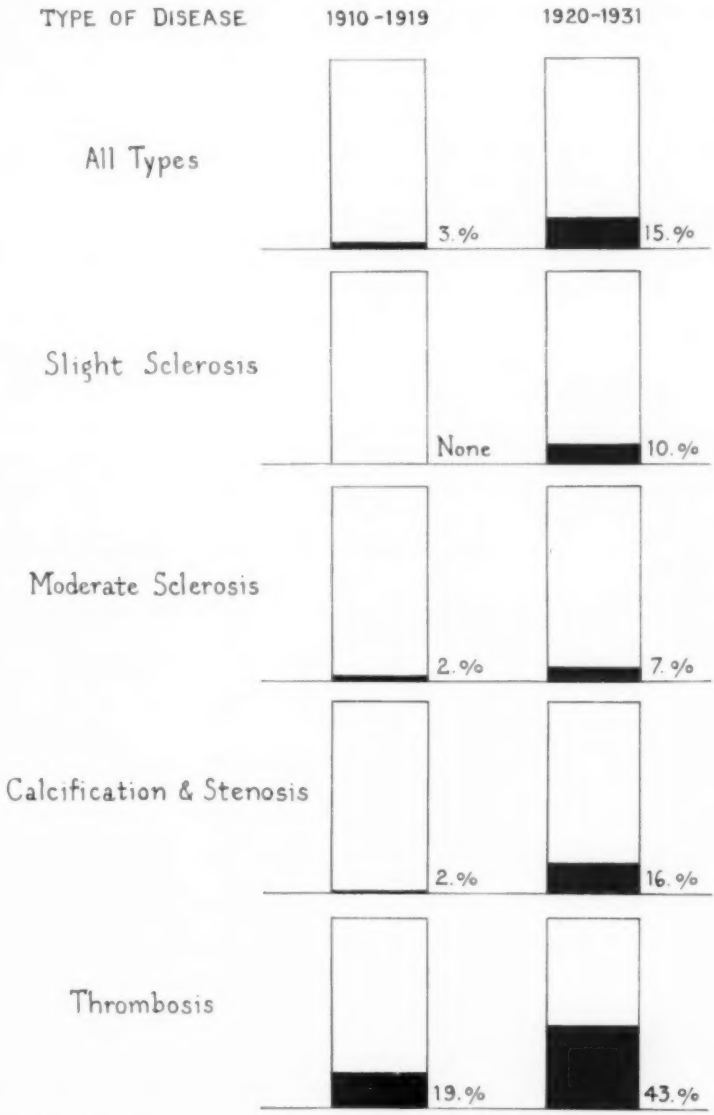

FIG. 5.—Per cent of total autopsies showing coronary disease, recognized clinically, 1910–1931, in two periods.

ness, the causes of death have been divided into "primary" and "secondary."

Primary Cause of Death. By this term is meant the disease which may be regarded as the basic pathologic condition. The designations in Table 8 are, for the most part, self-explanatory. Arteriosclerotic cardiovascular disease includes degenerative changes not only in the vessels of the heart but also elsewhere in the arterial tree. A separate group has been made of the cases with arteriosclerosis of the kidneys because they presented a clearly defined clinical picture, which differed sharply from the instances of glomerulonephritis. The latter showed, at autopsy, definite inflammatory changes in the glomeruli.

TABLE 8.—INCIDENCE OF PRIMARY CAUSES OF DEATH, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910–1931.

Primary cause of death.	No. of cases.*				Per cent of total cases.			
	Total	25–44	45–64	65 and over	Total	25–44	45–64	65 and over
Total—All causes	746	133	408	194	100.0	100.0	100.0	100.0
Rheumatic heart disease	39	17	16	2	5.2	12.8	3.9	1.0
Arteriosclerotic cardiovascular disease	191	18	116	57	25.6	13.5	28.4	29.4
Syphilitic aortitis	53	22	29	1	7.1	16.5	7.1	0.5
Pneumonia	43	6	21	16	5.8	4.5	5.1	8.2
Malignant disease	119	7	67	45	16.0	5.3	16.4	23.2
Tuberculosis	15	1	9	5	2.0	0.8	2.2	2.6
Acute abdominal condition	81	9	41	31	10.9	6.8	10.0	16.0
Sepsis	30	6	18	5	4.0	4.5	4.4	2.6
Glomerulonephritis	40	26	9	2	5.4	19.5	2.2	1.0
Arteriosclerosis of kidneys	45	12	28	5	6.0	9.0	6.9	2.6
Hyperthyroidism	3	...	3	...	0.4	.....	0.7	
Disease of hematopoietic system	15	1	7	7	2.0	0.8	1.7	3.6
Diabetes mellitus	22	...	16	6	2.9	.....	3.9	3.1
Trauma	2	...	1	1	0.3	.....	0.2	0.5
Disease of liver	10	...	7	3	1.3	.....	1.7	1.5
Other disease	38	8	20	8	5.1	6.0	4.9	4.1

* Age group "0–24" has been omitted because it comprised only 11 cases.

Rheumatic heart disease, as might be anticipated, occurred chiefly in the young and caused death in but a small number. Arteriosclerotic cardiovascular disease was the principal primary cause of death (25.6 per cent of the total) and these patients died mainly after 45 years of age. Syphilitic aortitis was the chief lesion in 7.1 per cent, and death occurred, for the most part, between the 25th and 44th years. Malignant disease, occurring, like arteriosclerosis, in later life, was numerically second as the cause of death (16 per cent). Glomerulonephritis carried off chiefly the younger

patients, in contradistinction to arteriosclerosis of the kidneys which caused the death of the more mature. It appears that pathologic change in the coronary arteries may be found as an associated condition in a variety of fatal diseases and over a wide age range.

Secondary (Immediate) Cause of Death. This term is used to designate the condition which was directly responsible for the final catastrophe. For example, the primary disease may have been diabetes; the immediate cause of death, sepsis.

In a series of cases selected primarily because they showed lesions in the coronary arteries, it was reasonable to expect that heart failure should be the most frequent terminal event. And so, in Table 9, it appears that, at all ages, cardiac insufficiency led as the immediate cause of death. Sepsis came second, pneumonia third and uremia fourth. In the younger age groups (25 to 44), however, death from renal insufficiency resulting from glomerulonephritis was second only to that from heart failure. In the aged, sepsis and pneumonia more often terminated life.

TABLE 9.—INCIDENCE OF SECONDARY (IMMEDIATE) CAUSES OF DEATH, BY AGE GROUPS, IN 746 AUTOPSIES ON CASES WITH CORONARY DISEASE, 1910–1931.

Secondary (immediate) cause of death	No. of cases.*				Per cent of total cases.			
	Total	25–44	45–64	65 and over	Total	25–44	45–64	65 and over
Total—All causes	746	133	408	194	100.0	100.0	100.0	100.0
Cardiac insufficiency	314	62	168	80	42.0	46.6	40.7	41.2
Uremia	74	29	35	7	9.9	21.8	8.6	3.6
Acidosis (diabetic)	4	...	4	...	0.5	.....	1.0	
Pulmonary embolism	21	2	16	3	2.8	1.5	3.9	1.5
Cerebral embolism	8	...	6	2	1.1	.....	1.5	1.0
Cerebral hemorrhage	27	2	19	6	3.6	1.5	4.7	3.1
Pneumonia	109	10	55	44	14.6	7.5	13.5	22.7
Sepsis	148	21	82	42	19.8	15.7	20.1	21.6
Aneurysm of aorta	11	4	5	2	1.5	3.0	1.2	1.0
Other disease	30	3	18	8	4.0	2.2	4.4	4.1

* Age group "0–24" has been omitted because it comprised only 11 cases.

Summary. 1. A statistical analysis was made of the autopsy and clinical records of 762 cases of coronary artery disease observed at the Presbyterian Hospital during the period 1910 to 1931. The facts apparent as a result of this survey are to be regarded as applying to this material; no general conclusions are drawn.

2. Arteriosclerosis was the most common lesion, having been found in 97.2 per cent of the cases. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the coronary blood flow in 5.7 per cent.

3. Syphilis did not play a rôle in predisposing to coronary sclerosis. It was present no more frequently in patients with coronary disease than in those without it.

4. In 2877 consecutive autopsies, lesions of the coronary arteries were found in 25.9 per cent. This is a strikingly high figure.

5. In half of the cases showing sclerosis in the coronaries, the lesions were "slight" or "moderate;" in many of these instances, no functional impairment of the cardiac circulation was induced by such lesions. The lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developed with advancing years.

6. In this series of autopsies, the incidence of coronary disease showed a slight but steady increase throughout a 22-year period; but the increase was not nearly so great in the proven cases as was indicated by the figures based on clinical diagnosis alone. The reasons in explanation of these facts have been given.

7. Coronary artery disease increased at all ages, but the increase was particularly noteworthy between the ages 25 and 44. There was a predominance of males. The number of cases increased in both sexes.

8. Occupation did not appear to play a significant part in determining those whose vessels were affected. The largest percentage of coronary cases was found among foremen and skilled workers.

9. The clinical diagnosis of coronary disease is being made with greater accuracy as well as with increased frequency. Many cases are latent and probably cannot be recognized during life. Even in the presence of calcification or stenosis, the diagnosis was made clinically in but 16 per cent of the cases during the years 1920 to 1931. During this same period, coronary thrombosis was correctly diagnosticated in only 43 per cent of the cases.

10. Arteriosclerotic heart disease was the most frequent primary cause of death. Cardiac insufficiency was the commonest terminal event.

11. The increase in the incidence of affections of the coronary arteries is not to be regarded as a matter of concern. Rather should it be a source of satisfaction that, due largely to effective control of infectious diseases, men may survive to an age when disorders incident to senescence lead to the termination of life.

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THE DIFFERENTIATION OF ACUTE CORONARY ARTERY THROMBOSIS FROM PULMONARY EMBOLIZATION.

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Pulmonary embolism may be the cause of a syndrome characterized by intrathoracic oppression or pain, dyspnea, cyanosis, shock, and sometimes sudden death. This syndrome closely resembles the clinical picture of acute coronary artery thrombosis. In 1908 Von Neusser[1] in his truly remarkable lectures on angina pectoris commented on the necessity for differentiating "paroxysmal sternocardiac pain" from the syndrome of pulmonary embolization. No further conspicuous discussion of this problem appeared in the literature until a very recent communication by Hamburger and Saphir.[2] They reported 5 cases with autopsies and remarked on the need for a more general recognition of this problem in differential diagnosis.

In the past 3 years we have collected the following 6 cases who were presumed to have had fatal attacks of coronary artery thrombosis but in whom necropsy revealed that they had succumbed to pulmonary embolization. In 2 instances the diagnosis was made particularly difficult by the fact that coronary artery disease had previously been present, and its existence was confirmed by the history, physical and laboratory findings. The fatal episode, on the other hand, was caused by a pulmonary embolus and not by the primary vascular disease of the heart. In the other 4 cases no previous clinical or laboratory evidence of coronary artery disease had been present, but the cause of death ascribed to coronary thrombosis was shown by autopsy to be due to pulmonary embolus.

Presentation of Cases. Case 1.—R. J., a woman, aged 55, was admitted for precordial pain starting that morning. Six months before, she suddenly experienced agonizing precordial pain radiating to the left scapular region and accompanied by dyspnea, orthopnea and weakness. There were several recurrences of this syndrome after the first attack. Recently there had been some right lower extremity pain with transient swelling of the limb. Examination revealed an acutely ill elderly female, dyspneic and complaining of chest pain. The lungs were emphysematous and there were some inconstant râles at the right base. The heart was greatly enlarged to both right and left. Heart sounds were poor, but regular. A systolic apical murmur and a loud second aortic sound were present. The liver was enlarged to the umbilicus. There was no ascites. Blood pressure was 135 systolic and 85 diastolic. The blood Wassermann test was negative. The electrocardiogram showed left ventricular preponderance, negative T wave in Lead I, abnormal R–T segments, and widened and high Q–R–S complexes—resembling the record seen in long standing cases of arterial

hypertension. The diagnosis of coronary artery disease with myocardial insufficiency was thereby established.

Under observation the patient became more dyspneic, cyanotic and edematous. The right border of the heart percussed farther out. It was thought by the clinicians that the picture was caused by another coronary thrombosis.

Relevant Postmortem Findings (Dr. W. Kantrowitz). *Lungs.* The right lower lobe of the lung was the site of a large wedge-shaped hemorrhagic infarct which occupies practically the entire lobe. *The main branch of the pulmonary artery supplying this lobe was occluded by a large recent but adherent embolus.* The lungs were edematous.

Heart. Universal cardiac enlargement with adherent pericardium. On the anterior portion of the left ventricle, near the apex, was an old aneurysmal bulging of the wall with calcified margin. *The left anterior descending coronary artery was completely obliterated and calcified (old closure).* The *other coronary vessels showed arteriosclerotic changes and narrowing of their lumina but no closures.*

Saphenous Vein. The left saphenous vein was the site of a long thrombus, the proximal end of which showed a sharp breaking off. The vein proximal to the thrombus was empty.

Summary. (1) Coronary sclerosis with old closure and obliteration of left anterior descending artery and aneurysm of left ventricle with calcification; (2) pulmonary embolus with infarct of right lower lobe arising from the thrombosis of the left saphenous vein; (3) adherent pericarditis.

Comment. Case 1. With so clear a history of previous attacks of angina pectoris due to coronary artery disease, it was reasonable to interpret the last episode of chest pain as another attack. Both physical examination and electrocardiographic findings supported this diagnosis. Nevertheless, in retrospect, one point now appears worthy of mention which might have been of aid in directing attention to the possibility of a pulmonary embolism. The history of the recent occurrence of pain and swelling in a lower extremity should have suggested the possibility of an embolus from a venous thrombosis on the leg. However, in view of the minimal pulmonary signs, the absence of hemorrhagic sputum, and the inability to have this sick patient Roentgen-rayed, the diagnosis of pulmonary embolism, even if suspected, would have been difficult to prove. This case exemplifies the association in 1 patient of both conditions and the extreme difficulty of their clinical differentiation.

Case 2.—I. T., a clerk, aged 44, was admitted complaining of orthopnea, productive cough and (once) severe substernal pain with radiation down the left arm. He had consulted physicians 6 years before for intermittent claudication and they established the diagnosis of thrombo-angiitis obliterans. Gangrene in one small toe had necessitated amputation. Eight months previous to admission he had had attacks of precordial (not substernal) pain with radiation to the left shoulder and arm and occasionally to the right side. In the attacks initiated by effort and excitement—but also occurring while in bed—the patient was pale, perspiring, quiet, and had a sense of impending death. They lasted from 2 to 4 minutes, and relief was afforded by either sublingual medication of nitrites or hypodermic injections of morphin. After the first one he was incapacitated for 12 weeks and thereafter suffered from dyspnea on exertion. About 2 weeks before admission a series of similar attacks recurred.

Examination showed a well nourished and well developed man, dyspneic but not cyanotic. The pupils were active and there were some basal pulmonary râles. The heart sounds were of poor quality, the second pulmonic sound was louder than the second aortic and reduplicated. Occasional extra systoles were heard. The liver was soft and extended one finger breadth below the costal margin. The right fifth toe had been amputated; no arterial pulsations were present in either foot. The reflexes were normal. Blood pressure was 130 systolic and 64 diastolic. Urine and Wassermann tests were negative. The electrocardiogram showed the typical picture of an intraventricular conduction defect. It was felt that this patient had coronary artery disease with the syndrome of angina pectoris and that undoubtedly there had occurred some occlusions of small coronary vessels.

During a 10-day hospital stay the patient was free of any chest pain. While getting into bed from a wheel chair he suddenly developed an episode of paroxysmal dyspnea and cyanosis, became comatose and died. Several respirations occurred after the cessation of heart beats. This fatal episode was considered another attack of coronary thrombosis.

Relevant Postmortem Findings (Dr. L. Lichtenstien). *Lungs.* Scattered over the surfaces of both lungs there were large areas which were bluish-red in color and well demarcated from the adjoining aerated mottled areas. There was a hypercrepitant consistency to the lungs, indicating emphysema. *The pulmonary artery conus and both pulmonary branches contain soft embolic masses, grayish-red in color. They were not adherent. In both pulmonary arteries and in the small branches, particularly near the bifurcation, there were small adherent whitish-pink masses representing old organized emboli. Pulmonary veins were negative.*

Heart. The right ventricle was hypertrophied and dilated. On the lower half of the interventricular septum, extending to the apex, was an area of myocardial fibrosis 2 by 3 cm. The left ventricle was somewhat hypertrophied; myocardium was brownish-red in color with yellowish streaks. *The coronary arteries were patent and showed some intimal thickening with some narrowing of the left anterior descending and circumflex branch. No occlusions could be discovered.*

Summary. (1) Organized and recent bilateral pulmonary embolisms; (2) moderate sclerosis of left coronary artery with myocardial fibrosis; (3) pulmonary emphysema; (4) phlebitis, right iliac vein (?); (5) status after amputation of right fifth toe for gangrene (Thrombo-angiitis obliterans); (6) healed infarcts of spleen and kidneys; (7) brown induration of lungs.

Comment. Case 2. Although it has never been emphasized, the incidence of embolic phenomena in cases of extensive peripheral vascular involvement (arteries and veins) such as occurs in thromboangiitis obliterans is probably not uncommon. Coronary artery disease and coronary artery thrombosis are likewise frequent in this disease (Averbuck and Silbert[3]). Unquestionably this patient suffered many attacks of angina pectoris dependent upon coronary sclerosis. The seemingly typical nature of some of the attacks and the electrocardiographic findings gave adequate ground for this diagnosis and at autopsy a fibrotically replaced myocardial area was found. There was no fresh myocardial infarction or coronary artery thrombosis, however, to substantiate the clinical impression of a coronary occlusion. In view of the postmortem findings of fresh and old emboli in the pulmonary artery and branches, the conclusion is warranted that some of the attacks described in the

history were due to pulmonary emboli arising from the thrombotic process in the vessels of the lower extremities. Surely, the last attack—characterized by dyspnea and cyanosis, absence of pain and rapidly ensuing coma—was due to a pulmonary embolus.

Besides indicating a difficult diagnostic problem, this case illustrates that an individual may survive repeated small pulmonary embolizations. When many pulmonary artery branches become plugged additional emboli may prove fatal.

Case 3.—D. S., a housewife, aged 57, entered the Gynecological Service because of sticking pain in the left upper quadrant and an abdominal mass. Examination, study and biopsy established the diagnosis of adenocarcinoma of the rectum with coincident ovarian and pelvic carcinoma. Blood pressure was 152 systolic and 80 diastolic. Urine and Wassermann tests were negative.

Three days after her admission she awoke from her sleep complaining of precordial pain. She was dyspneic, cyanotic, cold, and terrified, with perspiring clammy extremities. The picture resembled shock with the pulse varying in quality to imperceptibility, systolic blood pressure ranging from 90 to 40, respiratory rate 46, and poor heart sounds. The heart appeared to be displaced to the left and bronchial breathing was heard over the right lung. Stimulation and oxygen were administered and the patient recovered somewhat. The precordial pain recurred a few hours later and radiation to the left arm was present at this time. *The clinical picture was explained on a basis of a coronary thrombosis with myocardial infarction.* Electrocardiogram showed the *T* wave in the third lead slightly inverted and cove shaped, the *T* waves in Leads I and II upright and coved. After another episode of precordial pain the patient ceased.

Relevant Autopsy Findings (Dr. E. B. Greenspan). *Lungs. A large reddish-black embolus filled up the pulmonary artery above the pulmonary cusps. The embolus then was broken and parts of this mass were found to be present in both the right and left pulmonary artery branches.* Pulmonary veins are negative.

Heart. The coronary arteries showed only slight arteriosclerotic flecking and the remainder of the heart appeared normal for this age. An ulcerating adenocarcinoma arising in the rectum and involving the regional lymph nodes and pelvic organs was present. There was extension of the growth into the inferior vena cava.

Summary. (1) Ulcerating adenocarcinoma of rectum with metastases to iliac nodes; (2) tumor extension into the inferior vena cava; (3) embolus in right heart, pulmonary conus and both branches of the pulmonary artery.

Comment. Case 3. There had been no operation in this case. The sudden onset of severe and recurring precordial pain with the typical "coronary" radiation, dyspnea, cyanosis, angor animi, and the general appearance of shock, all seemed to justify the diagnosis of a coronary thrombosis. Yet a few features which might have been of aid in the differentiation may be pointed out. Coronary thrombosis is rare in women unless associated with arterial hypertension or diabetes, neither of which was present in this instance. There was no previous history of any cardiac complaints or anginoid attacks. The electrocardiogram taken in the hospital during the last episodes did not show the usual changes seen in coronary artery closure. Aside from the picture of shock, dyspnea and cyanosis

were the outstanding signs. Lastly, there was unmistakable pelvic disease which predisposes to embolic phenomena. Although incapable of substantiation at that time, the diagnosis of pulmonary embolus was at least as likely to be correct as the diagnosis of coronary thrombosis.

Case 4.—S. F., a woman, aged 70, was admitted with a history that 5 days before admission while walking she experienced sudden substernal pain, without radiation, which caused great weakness and dyspnea. She had to go to bed. A chronic cough which she had had for many years now became painful. Orthopnea and dyspnea, some elevation of the temperature and ankle edema appeared. Hypertension was noted for the first time a day before admission. Examination revealed an acutely ill, obese, dyspneic, cyanotic female. Temperature was 100, pulse, 108, and respirations, 24. She was complaining of substernal pain. In the lungs there were some hypostatic râles at both bases, but no alteration in voice or breath sounds. The heart sounds were distant and poor in quality. The second pulmonic heart sound was louder than the aortic second sound; there were no friction rubs heard. No other noteworthy features appeared in the examination. Blood pressure was 150 systolic and 74 diastolic. Total leukocytes were 16,200, polymorphonuclears, 76 per cent; lymphocytes, 20 per cent; mononuclears, 4 per cent. Small amounts of sugar were present in the urine and the blood sugar was elevated. Blood CO_2–38 vol. per cent. The blood Wassermann test was negative. The electrocardiogram showed *T* waves in Leads I and II partly inverted with the *T* wave in Lead III low. The diagnosis was coronary artery thrombosis and diabetes mellitus. A day after her admission the temperature rose quickly to 105° F, the pulse and heart action became poor, the respirations more rapid and labored, and the patient ceased.

Relevant Autopsy Findings (Dr. E. B. Greenspan). The pulmonary arterial tree showed marked arteriosclerotic changes. *In the trunk of the right pulmonary artery, straddling its bifurcation, was a mass of adherent clots with extensions into several smaller arterial branches.* The heart was moderately enlarged and weighed 500 gm. The myocardium was pale and on cut section showed yellowish streaks of fat penetrating toward the endocardial surface. Small adherent thrombi were present in the auricular appendage and wall of the right ventricle which was distinctly hypertrophied. *The coronary arteries except for occasional yellow flecking showed no gross changes.*

Summary. (1) Embolus of right pulmonary artery and branches; (2) acute purulent bronchitis; (3) atherosclerosis of pulmonary arterial tree; (4) adherent small thrombi in the right auricle and ventricle.

Comment. Case 4. An attack of severe substernal pain in a 70-year-old woman who had diabetes mellitus surely warranted the diagnosis of coronary artery thrombosis. The suggestive electrocardiogram lent support to this diagnosis. In view of the autopsy findings, however, which failed to reveal a closed coronary artery but which showed a large pulmonary artery embolus, the absence of radiation of the pain and *the extreme dyspnea and cyanosis* become significant. Here again one can only learn that where the clinical picture of an assumed acute coronary thrombosis is not typical in most of its features the possibility of pulmonary embolization must be kept in mind, especially if cyanosis and dyspnea are marked and begin suddenly.

Case 5.—F. K., a woman, aged 59, was admitted with a 3-year history of shortness of breath, and orthopnea. She was known to have had arterial hypertension. Edema of the lower extremities made its first appearance 1 year before. A month previous to admission she had suffered an attack of grippe. She continued to cough after this illness. A few days before her admission to the hospital she suddenly became markedly cyanotic, dyspneic and stuporous. Upon admission she was almost comatose. *Cyanosis and dyspnea were both marked.* The heart was tremendously enlarged, particularly to the left. A systolic apical murmur and gallop rhythm were heard. All the peripheral pulses were present. Blood pressure was 100 systolic and 80 diastolic. There were signs of consolidation along with many râles over the lower left lung lobe. The liver was enlarged 4 finger-breadths below the costal margin, and there was pretibial edema. The condition did not improve in spite of active therapy, although a few hours after admission, the blood pressure rose again to 200 systolic and 110 diastolic. Electrocardiogram showed a tachycardia, left ventricular preponderance, and partial inversion of the *T* wave in Lead I. This state continued until death ensued.

She was considered to be a case of essential hypertension who had suffered a previous coronary closure (1 month ago) and who, before admission, again had sustained a major coronary artery occlusion which caused the fatal termination. The lung signs were interpreted as evidence of a confluent bronchopneumonia.

Relevant Autopsy Findings (Dr. J. Ehrlich). *Chest.* There was a massive effusion on the left side. The right side was free of adhesions or fluid. The right lung was voluminous, its pleura smooth. There was marked congestion and a large amount of fluid ran off the cut surface on slight pressure. The smaller branches of the pulmonary artery were thickened with raised yellowish intimal patches. The bronchi were congested and contained frothy brownish fluid. The left lung was completely atelectatic and represented by a small shrunken mass less than half the size of the right. The apical portion of the upper lobe was raised and firm and deep red in color. *On section a hemorrhagic, wedge shaped area was seen, the size of a pecan nut. One of the medium sized pulmonary arteries traced from the hilus to this area was occluded for a distance of about 2 cm. by a thrombus which, in its proximal portion, was rounded and hung free in the lumen of the vessel.* The occluded vessel does not present any gross disease of its wall exceeding that seen in the other vessels.

Heart. No increase in pericardial fluid. The left side of the heart was of tremendous size, globular in form and exceedingly firm. On opening the ventricles, the right heart was seen to be moderately dilated and hypertrophied. The left side had a small cavity and a wall 3½ cm. in thickness near the base. The myocardium did not show gross fibrosis or myomalacia. *The coronary arteries were moderately atherosclerotic, but everywhere patent.* There was atherosclerosis of the aortic and mitral valves and the aorta; the pulmonary valves were negative.

Summary. (1) Embolism of medium sized branch of pulmonary artery to left upper lobe; (2) hemorrhagic infarction of upper part of left upper lobe; (3) massive left pleural effusion; (4) marked hypertrophy of left ventricle; (5) coronary sclerosis, aortic and peripheral arteriosclerosis; (6) chronic passive congestion of liver and spleen; (7) early stage of arteriolar nephrocirrhosis.

Comment. Case 5. Here again the diagnosis of coronary artery thrombosis was justified in a woman of 59, known to have arterial hypertension. A large majority of patients with essential hypertension who die in cardiac failure have severe sclerosis of the coronary

arteries, frequently with thrombosis. Yet the history does not mention substernal pain, nor were there any previous anginoid attacks. The episode just before her death was characterized by the sudden onset of severe cyanosis and dyspnea, shock and stupor. There were signs of extensive pulmonary infiltration interpreted as signs of a confluent bronchopneumonia. Had the possibility of a pulmonary embolus been considered the points in the history enumerated above, in conjunction with the signs in the lungs, would have been of helpful diagnostic value.

Case 6.—R. G., a woman, aged 52, was admitted to the Surgical Service in November, 1931. She had had right upper quadrant pain for 19 years and jaundice for 6 weeks, with irregular fever, vomiting and one chill. She was a known diabetic. Examination showed a moderately icteric, obese female, who seemed to be comfortable. The heart and lungs were normal. The abdomen was obese, and the liver could be felt 3 finger-breadths below the costal margin. Slight epigastric tenderness was present. The gall bladder could not be felt. The uterus was prolapsed. The blood pressure was 150 systolic and 88 diastolic. The urinary sugar averaged about 1 per cent. The blood Wassermann test was negative. Diagnoses of cholelithiasis with cholecystitis, stone in the common duct, diabetes mellitus and prolapsus uteri were established. The patient was operated upon under spinal anesthesia supplemented by gas, oxygen and ether and the common duct was emptied of stones and drained. For a week after the operation convalescence proceeded satisfactorily. One afternoon the patient suddenly complained of severe precordial oppression and dyspnea. She became cyanotic and presented the picture of collapse. Because insulin was being administered thrice daily the possibility of insulin shock was considered. A blood sugar test of 120 mg., however, eliminated this possibility. Recovering from this episode, the patient did well for a few days. Five days later there occurred another attack of severe paroxysmal dyspnea, with cyanosis and shock. Pulse 146, respirations 48. In spite of active stimulation the patient went quickly into a coma and died.

Relevant Autopsy Finding (Dr. J. Ehrlich). *Lungs. The right pulmonary artery was filled with a coiled up, firm thrombus which was slightly adherent to the vessel wall and which extended for a short distance.* The clot had a fairly uniform diameter of ½ inch. No older, more adherent emboli were to be found in any of the smaller artery branches. No pulmonary infarctions. Pulmonary veins were normal.

Heart. The heart was flabby but not enlarged. Valves and endocardium were normal. In the right ventricle a coiled firm thrombus about 1 cm. in diameter and about 15 cm. in length was found lying free in the right ventricular cavity, situated mainly in the outflour tract. *Both coronary arteries were patent and did not show any thrombus or marked arteriosclerotic changes.*

Summary. (1) Embolism of right pulmonary artery and right ventricle; (2) status after choledochotomy and drainage.

Comment. Case 6. In this instance the circumstance of the insulin administration brought another possibility into consideration, that of insulin shock. The normal blood sugar level and the inability of the administration of orange juice to influence the symptoms quickly eliminated this possibility. The difficulty of certainly differentiating pulmonary embolization from a coronary closure

still remained. Of particular significance is the fact that the episodes occurred in an apparently healthy subject, postoperatively.

Discussion. The clinical picture of an acute coronary artery thrombosis is difficult to present briefly. The symptoms and signs depend upon the artery involved, the state of the other cardiac arteries and myocardium, and the reaction of the individual affected. Nevertheless, there are certain features which occur commonly. Severe substernal, epigastric or precordial pain which appears suddenly, perhaps radiating to the left or right shoulder, to the neck or to the jaw is frequent. Dyspnea need not be a pronounced symptom; it may be present in moderate degree. In the hyposensitive or in isolated left ventricular failure due to closure of a medium sized artery dyspnea can be severe. Often the breathing is shallow, rapid and restrained. With occlusion of a larger coronary vessel, cyanosis may be slight, patients presenting rather an ashen-gray color. Sweating, coldness of the extremities, a rapid thready pulse, diminished blood pressure, feeble heart sounds complete the general picture of shock. Sudden death is common. Pericardial friction rubs, basal lung râles or pulmonary edema occur.

Pulmonary embolus usually induces a syndrome characterized by the sudden appearance of painful oppression somewhere in the chest *with extreme cyanosis and dyspnea.* The pain has no typical radiation and often is of the type that can perhaps better be described as a strangling sensation, a sense of intrathoracic suffocation which provokes an angor animi as profound as that which occurs in angina pectoris or coronary thrombosis. In many cases shock accompanies the onset, and death occurs almost immediately. According to Edens[4] these sudden deaths are accounted for by vagal stimulation, the mechanical obstruction being insufficient. In those who survive the original shock, dyspnea and cyanosis, fever, and the appearance of pulmonary râles and abnormal breathing constitute the clinical picture. In other cases the heart fails comparatively rapidly. Increasing cyanosis, quickly enlarging liver, and dilatation of the heart to the right signify the right ventricular failure. Cough with the expectoration of sanguineous sputum, pleural rubs and painful respiration depend upon the branch of the pulmonary artery and the area of lung involved. Recovery is not uncommon.

It is thus obvious how confusion in the diagnosis of these two syndromes might readily result. Accurate diagnosis becomes even more difficult in the frequent atypical forms. For instance, as has been emphasized by Libman,[5] hyposensitive individuals may suffer a coronary artery closure without pain, but demonstrate a severe dyspnea instead. On the other hand pulmonary emboli may cause severe pain in the left side of the chest, or occur without hemoptysis. Such cases as well as those with little cyanosis and dyspnea, because of rapidly ensuing shock, present the most difficult problems in differential diagnosis.

There is little to be gained by an extended discussion of theoretical factors that might aid in distinguishing these two conditions. A review of the clinical histories presented in the light of the autopsy findings suggests some general points which would seem to promise real help if applied to future cases.

When the clinical picture suggesting coronary artery thrombosis occurs in a female patient who has neither arterial hypertension nor diabetes, a pulmonary embolus should be suspected. The high incidence of embolic phenomena in the female sex arising from abnormal pelvic conditions is an important factor in this connection. If the history or physical examination brings to light existent or previous evidence of peripheral vascular involvement, *i. e.*, phlebitis, unilateral leg edema, pelvic disease or lower extremity abnormalities, the likelihood of the coronary syndrome being caused by an embolus to the lungs is strengthened.

Occurring postoperatively, the clinical picture of pulmonary embolus readily simulates coronary thrombosis. When it is recalled that pulmonary emboli are very frequent after operation and that coronary artery thrombosis is comparatively rare because patients with coronary artery disease are spared any but emergency surgical procedures, such cases will be correctly analyzed. One should only cautiously advance the diagnosis of coronary thrombosis in a patient presenting the syndrome under consideration who does not give a history suggesting coronary artery disease, *i. e.*, anginal attacks, "gastric" symptoms, etc. Levine[6] was able to obtain such information in the majority of cases he studied and he lays great stress on the value of this data in diagnosis. Pulmonary embolism may explain the syndrome in such an instance.

Finally, in a hyposensitive individual, when the diagnosis of coronary artery thrombosis is made in the absence of pain, and dyspnea is an outstanding sign, the possibility of a pulmonary embolus must be excluded. Here, too, severe dyspnea and marked cyanosis, even in the presence of pain, should direct attention to this diagnosis. For these signs are the most striking and characteristic of pulmonary embolus. The dyspnea is severe, taking the form of rapid stertorous breathing, signifying a genuine air hunger. The cyanosis is usually very marked and usually exceeds that of coronary artery thrombosis. Unfortunately, the location and radiation of the pain in coronary artery thrombosis are so variable that from these features alone in any given case differentiation cannot be made from the intrathoracic pain induced by a pulmonary embolus.

The conditions may coëxist, as exemplified in our Cases 1 and 2. Coronary artery occlusion with resulting myomalacia cordis is not infrequently the cause of ventricular mural thrombosis. As the left anterior descending branch of the left coronary artery is the one most commonly involved, and according to Gross[7] supplies

small parts of the right ventricle and the septum, right ventricular mural thrombosis may occur after left coronary artery occlusion. Therefore, pulmonary emboli may readily complicate this condition. When both conditions are present, the association outlined above does not necessarily hold. In both of our cases illustrating this association the origin was not intracardiac, but in the lower extremities. Nevertheless, wherever the emboli arise, the symptoms caused by a pulmonary embolus in a patient who has proved coronary disease may so simulate a coronary occlusion as to be impossible of differentiation. Unless the manifestations of the embolus are typical, with right side chest pain, pleural rubs and hemoptysis, the condition goes unrecognized, to be disclosed only in the pathologic study. Differentiation in this kind of case is perhaps of pure academic interest and it suffices here merely to point out the problem involved.

In addition to the above discussed clinical features, one must consider in the differential diagnosis the help offered by various laboratory investigations. The rise in the leukocyte count which follows coronary thrombosis with infarction of the myocardium also occurs in pulmonary infarction resulting from pulmonary emboli (Libman and Sacks[8]). Thus the blood count cannot be of definite aid in differentiation.

Roentgen ray films of the lungs always serve as an important means of determining the presence of pulmonary lesions. Unfortunately the gravity of the general condition of these patients usually contraindicates this procedure.

To determine differentiating criteria, Anderson[9] recently investigated the electrocardiographic findings in experimentally induced pulmonary embolism in dogs. He found fairly consistent changes such as "tachycardia with disturbance of S–T segments with inverted T waves. Coronary T waves were encountered only once. The work suggests a rather more rigid requirement for the electrocardiographic diagnosis of coronary thrombosis but whether the tracings are sufficiently differentiated to warrant electrocardiographic diagnoses of pulmonary embolism is uncertain." His paper is available only in abstract, but it is safe to say that similar studies should be repeated on man in order to establish the electrocardiographic changes in pulmonary embolism. Pathologic studies must also be undertaken in order to correlate the artery and lung involvement with the electrocardiographic findings.

Aside from the desirability of interpreting the manifestations of disease states as accurately as possible, the differentiation of pulmonary embolization from coronary thrombosis has a practical aspect. Pulmonary emboli have been successfully removed surgically by Kirschner[10] and by Meyer,[11] who used the method first described by Trendelenburg.[12] With improvements in technique and more clearly defined indications, it may be possible in the

future to deal with more of these pulmonary embolic accidents in this radical manner.

Summary. Pulmonary embolus may cause a clinical picture indistinguishable from the syndrome of an acute coronary artery thrombosis. The case records and autopsy findings are presented of 6 patients in whom this problem in diagnosis occurred. In 2 the conditions coëxisted. Some points of possible aid in differentiation are discussed. The possibility of successful surgical removal of pulmonary emboli, as well as other differences in treatment, makes this problem more than one of purely academic or diagnostic importance.

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RENAL AMYLOIDOSIS IN RELATION TO RENAL INSUFFICIENCY.

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Much conflicting evidence has been brought forth in the numerous case reports in the literature in which various interpretations have been given to the occasional occurrence of renal insufficiency in renal amyloidosis. Some have regarded the renal insufficiency found at times in amyloidosis of the kidneys as coincidental, and much is said of amyloid admixture with other well recognized forms of renal disease. Others have regarded the occurrence of renal insufficiency as a part of renal amyloid disease itself in its later stages, thus simplifying the pathologic concept in an attempt to explain both physiologic and pathologic changes on the basis of a single disease entity.

In view of the active interest in this subject and the various interpretations given to it in the literature, a study of 100 cases of renal

amyloid disease which came to autopsy in the Philadelphia General and University of Pennsylvania Hospitals during the last 12 years is presented here. Particular emphasis has been placed on the presence or absence of renal insufficiency and the interpretation of its presence in the light of the gross and microscopic appearance of the kidneys.

Method of Study. One hundred unselected cases of renal amyloidosis were studied and correlated with the clinical records, including a survey of the various underlying etiologic diseases, age incidence, blood pressure readings, weight of heart, presence or absence of edema, urinalyses, blood chemical studies and other clinical evidences of renal insufficiency.

In the 9613 autopsies performed between the years 1920 and 1932, amyloid was found in the kidneys in exactly 100 cases. In this series renal amyloidosis was found to occur between the ages of 11 and 82, with the highest incidence in the 3d decade (Table 1). In 2 instances, amyloid was found in the kidneys and not in the liver or spleen, contrary to the more common finding of extensive deposits of amyloid in the latter organs with little or none in the kidneys.

Chronic ulcerative pulmonary tuberculosis was found in 70 per cent of the cases, which is in keeping with the well known fact that the most common cause of amyloidosis is chronic suppuration, particularly that secondary to and implanted upon tuberculosis. The incidence of the probable etiologic diseases in the remainder of the cases is shown in Table 2. The clinical duration of the etiologic disease was 1 year or more in 64 cases, while in 8 cases the duration was 6 months to 1 year. Eight patients gave a history of having had the etiologic disease for a period of only 3 to 6 months. In the remainder of the cases no definite history was obtained as to the duration of the disease which was considered to be the cause of the amyloidosis.

TABLE 1.—AGE INCIDENCE

(Number and Per Cent).

11 to 20 years	9
21 to 30 years	27
31 to 40 years	18
41 to 50 years	19
51 to 60 years	13
61 to 70 years	9
71 to 82 years	5

TABLE 2.—ETIOLOGIC DISEASE

(Number and Per Cent).

Pulmonary tuberculosis	70
Tuberculosis of bone	8
Malignant tumors	9
Empyema	5
Chronic arthritis	2
Chronic osteomyelitis	1
Bronchiectasis	1
Lung abscess	1
Cause unknown	3

Blood urea nitrogen determinations were made in 46 of the 100 cases. As is shown in Table 3, 34 cases had readings below 35 mg. per 100 cc. In 5 the blood urea nitrogen ranged from 40 to 60 mg., and in 3 from 61 to 100 mg. In only 4 cases was the blood urea nitrogen over 100. Those which showed a blood urea nitrogen of over 35 mg. per 100 cc. were arbitrarily considered as cases associated

with renal insufficiency. Of the 46 cases 12 had this evidence of impaired renal function. How many of the remaining 54 would have shown an elevation in the blood urea nitrogen, had blood studies been carried out, it is of course impossible to say. However, no evidence is given in the clinical record or clinical diagnosis of these 54 cases to suggest that renal insufficiency existed, and it is perhaps for this reason that blood studies were not made. This omission, as well as omissions of adequate blood pressure readings, other renal function tests and complete urinalyses are indeed unfortunate, yet they must be expected in making a retrograde study of such a series of cases.

TABLE 3.—BLOOD UREA NITROGEN DETERMINATIONS (46 CASES).

	Cases.	Per cent.
Below 20 mg. per 100 cc.	26	56
Between 20 and 30	7	15
31 and 35	1	2
36 and 40	1	2
41 and 60	4	9
61 and 100	3	6
Over 100	4	9

Blood pressure readings were recorded in 35 cases (Table 4). Of these, 20 had a systolic pressure below 120, 11 had a systolic pressure between 120 and 150 and in 4 the systolic pressure ranged from 150 to 180. If a systolic pressure above 150 is taken as evidence of arterial hypertension, this condition may be said to have existed in 12 per cent of the 34 cases. In the 4 cases in which hypertension occurred, the kidneys showed arteriolar nephrosclerosis of moderate degree. In 1 case a large amount of amyloid was present in the kidneys and there was evidence of impairment of renal function as shown by a blood urea-nitrogen reading of 162 mg. per 100 cc. In the other 3 cases amyloid was present in relatively small amounts and there was no evidence to show that renal insufficiency existed.

TABLE 4.—BLOOD PRESSURE READINGS.

	Cases.	Per cent.
Below 120 (systolic)	20	57
Between 120 and 150	11	31
Between 150 and 180	4	12
Total cases	35	

The phenolsulphonephthalein excretion was definitely impaired in only 2 of the 5 cases in which this test was performed. Three showed an excretion of over 50 per cent of the dye in 2 hours, while in the other 2 cases the percentage of the excretion was 33 and 15 respectively.

Blood creatinin determinations were made in 7 cases (Table 5) and of these 5 showed 3 mg. or less per 100 cc. In 2 cases the readings were 5.3 and 10 mg. An analysis of the table shows that in only 2 instances was there a definite elevation of both the blood creatinin

and the blood urea nitrogen. As was to be expected, in the 3 cases in which the blood urea nitrogen was only moderately elevated, the creatinin readings were within normal limits.

TABLE 5.—COMPARISON OF B. U. N. AND CREATININ READINGS (7 CASES).

B. U. N., mg. per 100 cc.	Creatinin, mg. per 100 cc.
12	1.3
20	1.2
40	1.6
60	2.3
70	3.0
102	5.3
150	10.0

Qualitative tests for albumin in the urine were recorded in 84 cases. No albumin was found in 7; the remainder (92 per cent) showed albumin varying in quantity from a trace to large amounts.

The specific gravity of the urine was recorded in 72 cases. Twenty-three (32 per cent) showed readings all below 1.020. A specific gravity of 1.020 or greater was observed in the remainder of the cases.

The urine had been examined for casts in 63 cases. These were found to be present in 50 cases (79 per cent), while in 13 (21 per cent) they were absent. In most instances, no mention was made in the records as to the number or kinds of casts seen and no attempt has been made therefore to correlate these in the present survey.

Edema was mentioned as present in 24 of the 100 cases. In most instances, it was slight and confined principally to the lower extremities.

Table 6 gives an analysis of 91 cases in which the combined kidney weight was recorded. These weights, averaging 391 gm., are in keeping with the usual finding that in amyloid disease the kidneys are larger than normal.

TABLE 6.—COMBINED KIDNEY WEIGHTS.

Grams.	Cases.	Approximate per cent.
Below 200	2	2
Between 200 and 300	20	22
301 and 400	33	36
401 and 500	23	25
501 and 600	6	6
601 and 700	3	3
701 and 800	4	4

The size of the heart was usually small or within normal limits (Table 7). If 350 gm. is taken as the upper limit of normal, then 16 cases showed cardiac hypertrophy. In 5 of these, cardiac lesions were found which could well account for this hypertrophy without invoking renal amyloidosis as a cause: 2 had pericardial adhesions, 2 mitral stenosis and 1 had aortic insufficiency.

Since this study is primarily concerned with the occurrence of renal insufficiency in amyloidosis of the kidneys, especial attention

was paid to cases which gave evidence of impairment of renal function. The basis for considering that renal insufficiency existed was an elevation of the blood urea nitrogen above 35 mg. per 100 cc. Data on blood creatinin, phenolsulphonephthalein excretion and the concentrating power of the kidneys were not complete enough to be cited as evidences of renal insufficiency. On the basis of the

TABLE 7.—HEART WEIGHTS IN 100 CASES.

Grams.	Cases.
150 to 250	51
251 to 350	33
351 to 400	4
401 to 500	8
501 to 600	2
Over 600	2

standard above noted, 12 cases of renal amyloidosis were found to be associated with renal insufficiency (Table 8).

The 12 cases associated with renal insufficiency were studied in detail both grossly and histologically in an attempt to learn if amyloid disease itself, in its later stages, can account for renal insufficiency without admixture of other bilateral inflammatory or degenerative disease of the kidney. Several stains were employed: hematoxylin and eosin, methyl violet and Congo red; the latter two being specific stains for amyloid.

With experience, it is usually not difficult to separate the characteristic microscopic picture of renal amyloidosis causing impairment of kidney function from that of other kidney disease usually associated with renal insufficiency. Seven (Nos. 1, 5, 7, 8, 9, 10, 12) (Table 8) of the former type were found after a thorough review of the sections from the kidneys of the above 12 cases. The histologic picture was correlated with the gross description of the kidneys. The kidneys were of average size or moderately enlarged, firmer in consistency than normal and the cortical surface was uniformly coarsely granular and pale gray in color. The resistance to cutting was definitely increased and the cut surface was pale gray and fibrous in appearance. In some instances the cortex was not distinguishable from the medulla, while in others the cortex was moderately narrowed and fairly well demarcated from the medulla.

Microscopically, the architecture was greatly altered by an irregular overgrowth of dense fibrous tissue which was infiltrated with a few lymphocytes, and occasionally contained homogeneous material which gave the amyloid staining reaction. Most of the glomeruli were filled with amyloid which completely obliterated the capillary bed. These glomeruli were considerably increased in size, some up to twice normal. A few were of average size and contained relatively small amounts of amyloid, which appeared to obstruct only a few of the capillaries of the tuft. In a few sections the glomeruli containing amyloid showed moderate thickening of

TABLE 8.—SUMMARY OF 12 CASES SHOWING RENAL INSUFFICIENCY.

Series No.	Autopsy No.	Etiologic disease.	Duration (yrs.)	Age.	Sex.	Col.	Blood urea N (mg.).	Creatinin (mg.).	P.S.P.	B. P.	Urine.			Weight heart (gm.).	Comb. weight kidneys (gm.).	Edema.
											Sp. gr.	Alb.	Casts			
1	31–662	Tbc. of hip	8	40	M.	W.	180	....	....	104/60	....	....	....	290	290	0
2	30–213	Arthritis deformans	12	43	M.	W.	70	....	....	....	....	+	....	500	715	0
3	30–31	Chr. osteomyelitis	7	27	M.	W.	102	5.3	....	....	1010 (fixed)	Trace	+	210	525	0
4	29–421	Chronic arthritis	11	41	M.	W.	150	10	....	106/58	1015	++	....	350	360	0
5	27–195	Pulmonary Tbc.	4	19	F.	W.	50	....	....	130/90	1019	0	+	190	520	+
6	24–423	Hypernephroma	2	56	M.	W.	162	....	....	175/95	1022	+	+	450	550	0
7	24–19	Pulmonary Tbc.	1	61	M.	W.	60	2.3	....	95/45	....	....	....	350	320	0
8	23–567	Pulmonary Tbc.	1½	21	M.	B.	40	1.6	13%	....	1020	++	++	240	430	0
9	31-125	Lung abscess	?	33	M.	B.	65	....	....	100/80	....	++	++	390	490	0
10	20–392	?	?	19	M.	W.	72	....	....	118/90	1010	+	....	320	650	Slight.
11	32–34	Pulmonary Tbc.	2	34	M.	W.	45	....	....	80/40	....	++	....	150	300	0
12	31–827	Pulmonary Tbc.	?	65	M.	W.	70	3	....	110/70	1009	+++	....	300	240	0

the capsule of Bowman, but "crescent formation" was not noted, although there were adhesions between the tuft and the capsule. In the areas of dense fibrosis there was marked atrophy or complete disappearance of the tubules. These were thought to represent in large part the tubules leading from the glomeruli which were damaged or destroyed. In the areas where the fibrosis was not so marked, the tubules were greatly dilated and the lining epithelium was flattened. Casts were seen in many of the tubules. A few sections showed the medulla to contain deposits of amyloid around the tubules and in the walls of the small arteries. Some of the sections showed the walls of the larger arteries to be moderately thickened, but this change was most marked in the arterioles. Material which stained for amyloid was seen in the walls, causing the lumina to be narrowed.

This histologic picture of renal amyloidosis in its late stages is similar in some respects to that of the small granular kidney of chronic glomerulonephritis and in the later stages of arteriolar nephrosclerosis, mainly in the alteration of the architecture by the irregular overgrowth of fibrous tissue in the stroma, lymphocytic infiltration in the patches of fibrosis, and dilatation or atrophy of tubules.

In late amyloid disease resulting in renal insufficiency, amyloid is present in such massive amounts that the capillary bed of many glomeruli is occluded. The glomeruli containing amyloid are somewhat larger than normal and as a rule there is slight thickening of the capsule of Bowman and no proliferation of the cells of the glomerular tuft. The walls of the arterioles are definitely thickened and their lumina are narrowed; but in no case is complete obliteration of the lumen observed. The amyloid deposits are characteristically found in the media of the arterioles and the thickening of the wall of the vessel as a result of amyloid deposits in this coat results in narrowing of the lumen. In chronic glomerulonephritis the characteristic picture is the change in the glomeruli which are shrunken and often appear as balls of fibrous tissue showing complete or partial hyalinization and marked thickening of the capsule of Bowman. In advanced arteriolar nephrosclerosis, the arteriolar changes are conspicuous. The walls of the afferent arterioles are thickened and the lumina greatly narrowed and often completely obliterated. Here the thickening is the result of intimal sclerosis, while in the advanced stage of renal amyloidosis the thickening is principally the result of deposition of amyloid in the media of the vessels. In addition, the glomeruli show lobulation of the tufts, with slight thickening of the walls of the individual capillaries, and often present changes similar to those already described for chronic glomerulonephritis which result secondarily from loss of blood supply to them, due to occlusion of the afferent arterioles.

If all these facts are borne in mind, one can almost follow the pathogenesis of changes in the kidney, which finally result in insufficiency. It will also be seen that as each of the three conditions (amyloidosis, glomerulonephritis, arteriolar nephrosclerosis) increases in severity, the histologic pictures become more and more alike and difficult of separation, because the change which is common to them all, namely, the replacement fibrosis, becomes even more marked.

The remaining 5 of the 12 cases showing renal insufficiency could not with justification be classified in the group in which the renal insufficiency was attributed to the amyloid itself. Two of these (Cases 2 and 6) presented a picture so much like that of arteriolar nephrosclerosis, with a history and clinical findings that suggested antecedent nephrosclerosis, that the latter was regarded as the essential factor in the production of the renal insufficiency. The other 3 cases (Nos. 3, 4, 11) could not be classified from the standpoint of the histologic picture, not having either sufficient amyloid or the picture of non-amyloid renal disease to be placed in either of the above categories.

Discussion. It is generally believed that the occurrence of azotemia is relatively infrequent in amyloid disease of the kidneys. However, in this series of cases the condition occurred in 26 per cent of the 46 cases in which blood chemistry studies were made. Studies of the material from these cases corroborate the view of Troisier and his coworkers[1] that renal amyloidosis may manifest itself in several ways and that other degenerative and inflammatory diseases of the kidney may be simulated by amyloidosis in one or more of its stages. The main factor in the development of renal symptoms would appear to be the amount and extent of amyloid deposit in the kidneys. With little amyloid in the glomerulus there may or may not be enough injury to the glomerular capillaries to allow albumin to escape into the urine. With larger deposits of amyloid, there is more extensive injury to the glomerular capillaries and a larger amount of albumin escapes. In some instances the loss of this protein is great enough to result in a lowering of the osmotic pressure of the plasma, so that edema occurs. When the amyloid deposits are extensive, destruction of varying amounts of the renal parenchyma follows and renal insufficiency may ensue.

The destruction of the renal tissue and its replacement by fibrous tissue is apparently the result of obstruction of the afferent arteriole or occlusion of the capillaries of the glomerular tuft by deposits of amyloid. The tubules leading from destroyed glomeruli undergo atrophy and are replaced by fibrous tissue which results in a scarred and more or less contracted kidney similar in many respects to an advanced arteriolar nephrosclerosis or the late stage of chronic glomerulonephritis. Noble and Major[2] state that the pathologic process by which the kidneys in amyloid disease reach the state of

renal insufficiency shown in their cases is primarily one of vascular damage affecting the glomeruli most severely, but also involving the arteries of small caliber. They found the lumina of the afferent arterioles narrowed and the walls thickened by amyloid deposits, but in no case did they observe complete occlusion of the arterioles. In the present series, several cases were found which showed no significant changes in the afferent arterioles, while there were large deposits of amyloid in the glomeruli; which corroborates the view of these workers that the presence of amyloid in the glomerulus is the primary factor in the obstruction of the glomerular circulation, and in the resulting damage to the kidney and renal insufficiency.

In cases of renal insufficiency occurring with renal amyloidosis, the kidneys are usually described as being shrunken and scarred as a result of the extensive deposits of amyloid. None of the 12 cases of renal insufficiency in this series showed a reduction in the size of the kidneys. In 2 reported by Noble and Major, the kidneys showed no evidence of contraction and were unusually large. They considered the deposition of amyloid to have been so rapid that closure of capillaries and resulting azotemia occurred before contraction could take place.

The factors which enter into the clinical diagnosis of renal amyloidosis seem to be very variable, and it is not surprising that often the condition is not recognized until the patient comes to autopsy. Chronic glomerulonephritis is perhaps the most common diagnosis made in cases of unrecognized renal amyloidosis, especially when there is no apparent underlying disease to make one suspect the existence of amyloidosis. This was found to be true both in studies in the literature and in the cases studied in this survey. The material from these cases also supports Rosenberg's[3] statement that in the late stage of amyloid disease of the kidney the patient may run a course similar to that of the end stage of chronic glomerulonephritis with edema, slowly progressing renal insufficiency and an increasing azotemia. In amyloid disease, however, there is no hypertension or hypertrophy of the heart and nitrogen retention is not so marked as in chronic glomerulonephritis.

Bannick and Barker[4] state that renal amyloidosis has a clinical picture similar to that of chronic nephrosis but usually differs somewhat by the greater reduction in the excretion of phenolsulphonephthalein and in that there is likely to be some hematuria. They regard edema, hypercholesterolemia and hypoproteinemia as variable factors. The presence of hematuria, extrarenal sources of the blood being ruled out, eliminates the diagnosis of nephrosis. Christian[5] states that definite hematuria occurring in a patient showing the clinical picture of chronic nephrosis strongly indicates a definite form of glomerulonephritis. Abrami, *et al.*[6] found progressive azotemia possible, although exceptional, as the only manifestation of renal amyloidosis.

This study also supports Brulé's[7] contention that there is no special symptomatology of renal amyloidosis, as it is frequently associated with lipoid nephrosis and is often found in kidneys which show the lesions of glomerulonephritis. Shapiro[8] considers lipoid nephrosis and amyloidosis to be independent conditions and that either may be far advanced without the other existing. He states that amyloidosis when superimposed on lipoid nephrosis contributes to the renal damage and renders the prognosis grave. Abrami and his coworkers[9] feel that changes in the blood proteins and lipins are independent of the development of the amyloid process, since these changes are found with equal frequency in patients who do not have amyloid disease.

Polyuria is given as one of the early symptoms of renal amyloidosis by Labbé, *et al.*,[10] but this symptom may also be a prominent feature of arteriolar nephrosclerosis and chronic glomerulonephritis. According to Ellis and Weiss[11] the reabsorbing ability of the tubules may be impaired as a result of direct structural damage to the tubular cells themselves, and also as the result of conditions whereby excessively large amounts of glomerular filtrate pass rapidly down the tubules. They used as an example of the latter situation the kidneys in nephrosclerosis in which one-half of the glomeruli might be obliterated while the remainder would be comparatively unaffected. The normal glomeruli would greatly increase their individual filtration but this filtrate would be passing down one-half the usual number of tubules and the reabsorption of water would be decreased. The polyuria of renal amyloidosis can be similarly explained. In the present series there was not sufficient evidence on this point to warrant discussion.

The presence of albumin in the urine is a very common occurrence in renal amyloidosis (92 per cent in this series), and in a case with a suggestive disease background such as chronic tuberculosis, it may suggest amyloidosis, but of course is not sufficient in itself for a positive diagnosis. The common occurrence of albuminuria in all types of kidney disease makes it one of the least significant signs in the differential diagnosis of renal amyloid disease. Borromeo[12] considers variations in the amount of albumin in the urine to be important evidence of the presence of amyloid in the kidney. He reports a case in point which also had definite signs of cardiac decompensation with chronic passive congestion of the kidneys. The latter could easily have accounted for fluctuations in the amount of albumin in the urine.

Summary. 1. In 9613 consecutive autopsies, 100 cases of renal amyloidosis were found.

2. Tuberculosis of the lungs (70 per cent) and bones (8 per cent) was the etiologic disease in 78 per cent of the cases.

3. The highest incidence of renal amyloidosis occurred in the third decade of life.

4. Twelve of the 46 cases in which sufficient evidence was available were associated with renal insufficiency.

5. Obstruction of the glomerular capillaries by amyloid deposits is a factor in the causation of renal insufficiency.

6. Hypertension is relatively infrequent in amyloid disease of the kidney. Of 35 cases with blood-pressure readings, the systolic pressure was above 150 mm. in only 4 (12 per cent).

7. In the cases of renal amyloidosis with renal insufficiency, the kidneys were either normal in size or somewhat enlarged.

8. Renal amyloidosis may occasionally be associated with independent arteriolar nephrosclerosis.

9. Albuminuria is a fairly constant finding in renal amyloidosis.

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REVIEWS.

INDUSTRIAL HEALTH SERVICE. By LEVERETT DALE BRISTOL, M.D., DR.P.H., Health Director, American Telephone & Telegraph Co., New York City; formerly Commissioner of Health of the State of Maine, and Professor of Preventive Medicine and Public Health, University of Minnesota. Pp. 170. Philadelphia: Lea & Febiger, 1933. Price, $2.00.

THIS little book, which treats of the establishment and the management of an industrial health service, is written for the factory superintendent rather than the physician, but contains much which the physician starting in industrial work will find of value. The first part develops a well-balanced industrial health program. Parts II and III are suggestions as to management in the health instruction and problems of workers. Written in terse, simple style, the points are clearly presented. The author emphasizes particularly the importance of the public health aspect of medical supervision in industrial work and outlines the steps which will make this most effective.

The author believes that the management group in industry may participate actively in the health program and devotes considerable space in pointing out how this may be done. The short chapters which deal with common diseases and conditions common among workers might readily be used in health bulletins for general distribution in the factory.

W. C.

SURGICAL ANATOMY. By GRANT MASSIE, M.B., M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon, Guy's Hospital, etc. Pp. 458; 147 illustrations, many in color. Second edition. Philadelphia: Lea & Febiger, 1933. Price, $6.00.

A CONCISE and useful treatise on practical anatomy brought up to date. It should prove to be of interest to the student and general surgeon. The many illustrations are, for the most part, diagrammatic but none the less clear and informative. Confusion of nomenclature has been avoided by employment of both the old and the B. N. A. terminology.

G. W.

DIETETICS FOR THE CLINICIAN. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, in collaboration with RUTH LOTHROP GALLUP, Dietitian. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University. Pp. 666; 31 tables. Philadelphia: Lea & Febiger, 1933. Price, $6.50.

THE first 70 pages are devoted to the mechanics and physiology of digestion; the vitamin factors in diet; the classification, distribution and composition of foods; foods from the culinary standpoint. Then follow 465 pages on diet in specific diseases and conditions (alphabetically arranged) and on dietetics in pediatrics. (Some 18 physicians working in

various fields of clinical medicine have aided in preparing this part of the book.) The appendix (65 pages) contains recipes, information on supplementary methods of food and fluid administration; numerous tables (food composition, height and weight data, etc.).

Written for the general practitioner and the hospital intern, the subject matter is accurate, adequate, eminently practical and well presented. The book deserves emphatic recommendation. R. K.

THE GREAT DOCTORS. A Biographical History of Medicine. By HENRY E. SIGERIST, Professor of the History of Medicine, The Johns Hopkins University. Translated by EDEN and CEDAR PAUL. Pp. 436; illustrated. New York: W. W. Norton & Co., Inc., 1933. Price, $4.00.

IN 1931, the author published from Lehmann's house in Munich his "Grosse Aertze," a successful attempt to sketch the history of medicine through the portrayal of the lives of 55 leaders—from Imhotep to Ehrlich. To this translation, which has already had 3 printings in 1 year, another figure has been added—William Osler. Illustrative of the method is the division of the Osler section into 3 pages of development of the theme, "America entered the medical stage," and 3 more of a few salient details of Osler's life with a warm but correct appreciation of his influence. Like Lenard's "Grosse Naturforscher" and Almquist's "Grosse Biologen" in the same series, this work makes full use of the interest that all men have in personalities. While the author's method and charming style combine to make it interesting to lay and professional readers alike, his scholarship and scientific conscience keep the story from falling into the inaccuracies that mar so many recent popularized biographies.

E. K.

SPEECH DISORDERS. A Physiological Study of the Various Defects of Speech. By SARA M. STINCHFIELD, PH.D., Lecturer in Psychology, University of Southern California, Speech Clinic, Orthopaedic Hospital School, Los Angeles. Pp. 341, 8 plates of illustrations. New York: Harcourt, Brace & Co., 1933. Price, $4.00.

IN the opinion of this author, surveys indicate an increase of speech disorders. The text is divided into two parts. Part I includes a classification covering more than four pages (two disorders taken at random are rhinolalia uranoschismatica and paraphonia eunuchoidia). A chapter on Dysarthria Cerebropathica contains a large group of neuropsychiatric diseases. Part II gives statistical studies of the speech of 3000 college women and of public school groups. An interesting chapter is Personality, considered as Thurstone Personality Schedule and Trait Inventory. By reason of their fewer social distractions, Thurstone finds that neurotic students outstrip their well-adjusted classmates. The book is a useful contribution to speech literature. N. Y.

NEW INTRODUCTORY LECTURES ON PSYCHOANALYSIS. By SIGMUND FREUD, M.D., LL.D. Pp. 257; 1 illustration. New York: W. W. Norton & Co., Inc., 1933. Price, $3.00.

CONTINUING and supplementing earlier lectures, this volume considers dreams, the occult, anatomy of the mental personality, anxiety and instinctual life, psychology of women and a philosophy of life. Telepathy and thought transference, while not definitely endorsed, thread their way

through 27 pages of the text. The author complains that he is charged with things never said, such as, "the statement that all dreams are sexual." This seems to have been almost universally misunderstood.

The association tests of Jung are not mentioned and he cannot accept in its entirety the inferiority complex of that constructive analyst, Adler. Though names are prudently withheld, the following identities are unmistakable. Biographer Ludwig holds the withered arm of the ex-Kaiser responsible for an inferiority complex, said to figure so largely in the latter's psychologic life. The author differs, saying, instead of an excess of love that would naturally be accorded a disabled child, the proud mother withheld this love, which, in turn, caused the development of a relentless aversion toward the mother.

The charge that the author borrowed from Buddha on libido, from Plato on dreams and from others may show his good judgment. His presentations have taken hold on modern thought, and candor compels one to admit the desirability of psychoanalysis with modifications, in selected subjects, for a better understanding of certain cryptic thoughts, utterances and actions. N. Y.

THE DIAGNOSIS AND TREATMENT OF DIABETES. By W. WILSON INGRAM, M.C., M.D. (ABER.), Honorary Physician and Physician in Charge of the Clinic for Diabetes Mellitus, Royal North Shore Hospital, Sydney, etc.; and G. V. RUDD, M.Sc. (MELB.), Research Biochemist, Institute of Medical Research, Royal North Shore Hospital, Sydney. With a Preface by C. G. LAMBIE, M.C., M.D., F.R.C.P., F.R.S.E., Bosch Professor of Medicine, University of Sydney. Pp. 88; illustrated. Australia: Angus & Robertson, Ltd., 1933.

THIS small manual on diabetes and its treatment is unusual in that it is written for the physician and not the patient, with consequent omission of much elementary explanation. The chapters are devoted to definition, clinical considerations, laboratory diagnosis, diets, insulin and complications. While the subject matter is well and clearly presented, the small size of the book has resulted in some subjects being inadequately treated: 3 pages seem hardly enough for so important a part of diabetes as acidosis and coma. Seven set diets are given, ranging from 1100 to 2600 calories, with a list of foods, equal in value to a slice of bread, to be used for varying these diets.

The book is well worth reading even though it is written for use in Australia and the diets are arranged to suit the needs of people living in that climate. R. R.

DE VENARUM OSTIOLIS 1603 OF HIERONYMUS FABRICIUS OF AQUAPENDENTE (1533?–1619). Facsimile edition with Introduction, translation and Notes by K. J. FRANKLIN, D.M., Tutor and Lecturer in Physiology of Oriel College and University Demonstrator of Pharmacology, Oxford. Pp. 98; illustrated. Springfield, Ill.: Charles C Thomas, 1933. Price, $3.00.

THOSE who are fortunate enough to own an annotated translation and facsimile edition of Harvey's *De Motu Cordis*, such as Leake's edition put out by Thomas in 1928, should require no further stimulus toward the purchase of this work by Harvey's teacher. His detailed description and public demonstration at Padua of the valves in the veins (discovered a half century earlier) was undoubtedly one of the most important links in the chain of Harvey's argument. The present book, published by the History of Science Society, with the aid of a grant from the Carnegie

Corporation, includes an interesting biographic notice of Fabricius, accounts of early studies of the venous valves, and of the Anatomical Theatre at Padua, as well as a Bibliographic Note on the difficulties met in establishing the first edition of Fabricius' work. E. K.

NEUROLOGY. By ROY R. GRINKER, M.D., Associate Professor of Neurology, The University of Chicago. Pp. 979; 401 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $8.50.

THIS is the best recent book on neurology in English that we have seen. Logically conceived and structurally sound, it presents the subject as one phase of biology, rather than a dry detailing of the cause, pathology, symptoms, diagnosis and treatment of each nervous disease. Pains are taken to correlate structure and function as much as possible. It contains up-to-date information on such subjects as the histopathology of tumors, spinal fluid function and analysis, intracranial pressure, epilepsy, encephalitis, etc. The significance of the work of Sherrington and Magnus on reflexes is ably presented. The tables and diagrams are excellent and the illustrations well selected and well reproduced. The bibliography at the end of each section refers accurately to not only treatises but also specific monographs and journal articles. The index is accurate, as far as can be determined. E. T.

GREAT MEN OF SCIENCE. A History of Scientific Progress. By PHILIPP LENARD, formerly Professor of Physics and Director of the Radiological Institute in the University of Heidelberg; Nobel Laureate; Rumford Medallist of the Royal Society of London; Franklin Medallist of the Franklin Institute of Philadelphia. Translated from the second German edition by DR. H. STAFFORD HATFIELD. With a Preface by E. N. DaC. ANDRADE, Quain Professor of Physics in the University of London. Pp. 389; illustrated. New York: The Macmillan Company, 1933. Price, $3.00.

To those who accept that the history of medicine is inextricably interwoven with the history of science no excuse need be given for reviewing this book, even though Leonardo da Vinci is the only one of the 65 scientists whose work bears directly on medicine. Linnæus, J. R. Mayer, and Helmholtz, the only ones who appear to have completed medical studies, are all of the elect for their contributions to related subjects only. While it is perhaps chastening to physicians to realize how few of their own profession are included in such a list, and perhaps surprising to be reminded that other sciences have more claim than we to such familiar names as Boyle, Descartes, Newton, Black, Priestley, Darwin and others, still one might well ask why Hippocrates, Galen, Vesalius, Harvey, Morgagni, Bichat, Virchow and others did not have a right to be included. In a goodly company of chemists, Lavoisier is notable for his absence, though his name perforce appears often in the index.

The author, a distinguished pupil of Bunsen's and a Nobel Prize winner in physics, has succeeded in combining in a short space clear accounts of the contributions of these great men with personal pictures that present to us living personalities, sometimes human beings in error, but always struggling with more or less equanimity at their appointed problems toward the truth. To physicians the book may well be more stimulating than if more directly linked with their own field. E. K.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. VI. Tagung. Gehalten zu Würzburg am 6. und 7. März, 1933. By PROFESSOR DR. BRUNO KISCH, Köln. Pp. 276; 97 illustrations and 35 tables. Leipzig: Theodor Steinkopff, 1933. Price, Rm. 15.—

IN this sixth volume, according to the plan followed in this series (see Review, AM. J. MED. SCI., 1933, **185**, 427) whereby emphasis is laid on a certain phase of the problem, the relation of the nervous system is stressed. The chief addresses were by H. E. Hering, representing the laboratory side and F. Kauffmann for the clinical side. Studies in the most varied channels of this field are represented in 26 other articles. E. K.

HISTOLOGY. By S. RAMÓN-CAJAL, M.D. (MADRID), F.R.S. (LONDON), LL.D. (CLARKE), Director, Royal Cajal Institute for Medical Research; Emeritus Professor of Pathology, University of Madrid Faculty of Medicine; Nobel Premiate in Medicine; Life Senator of Spain. Revised by J. F. TELLO-MÚÑOZ, M.D. (MADRID), Professor of Pathology, University of Madrid Faculty of Medicine. Authorized translation from the tenth Spanish edition by M. FERNÁN-NÚÑEZ, M.D. (MADRID), Professor of Pathology, Marquette University Medical School. Pp. 738; 535 illustrations. Baltimore: William Wood & Co., 1933. Price, $8.00.

THIS translation is a welcome addition to current texts on the subject, both because of the novelty of many of the illustrations and of its fuller treatment of cytologic and neurohistologic topics. It offers the student of medicine his first opportunity of becoming acquainted, in English, with at least one aspect of the many-sided activities of the great Spanish histologist. Although the author has always been interested primarily in the nervous system, there is no part of the body which he and his students have not investigated by original methods. These results are reflected here, especially in the description of the tissues, which compose the major part of the book. The methods of general histology as well as those especially applicable to the nervous system are given ample consideration in 62 pages. These include the reduced silver methods for neurofibrils, in which the tissues are first immersed in silver nitrate, and then in a photographic developer, such as pyrogallic acid, when silver salts are formed within the nerve tissues. Nine methods for demonstrating neuroglia are given, among them those of Cajal, Río-Hortega and Schücarro. In all the descriptions, one sees the careful attention to detail, characteristic of the Madrid school. W. A.

CLINICAL SCIENCE INCORPORATING HEART. VOL. I, NO. 1. Edited by THOMAS LEWIS, M.D., F.R.S., aided in the selection of papers by T. R. ELLIOTT, M.D., F.R.S., R. T. GRANT, M.D., P. P. LAIDLAW, F.R.S., EDWARD MELLANBY, M.D., F.R.S., WILFRED TROTTER, M.S., F.R.S., and E. B. VERNEY, F.R.C.P. Pp. 158; illustrated. London: Shaw & Sons, Ltd., 1933. Price, 37/6.

Tempora mutantur and, of course, the publishers are wise in changing the name of this well-known journal to conform with the wider scope of its articles, even though for some time "related topics" have appeared happily under the old title. One always parts regretfully from an old friend, and it is perhaps with this as well as more practical considerations in mind that the publishers have maintained "Heart" in the largest letters on the cover. Of the 6 articles in this initial number—all from the University College Hospital—only 2 deal directly with cardiac problems. E. K.

LIFE IN THE MAKING. By DR. ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University. With the assistance of ELLERY RAND. Pp. 297; 8 illustrations. New York: The Viking Press, 1933. Price, $2.75.

WITH the gradual lifting of the sex tabu that this century is witnessing, the natural human interest in the generative process will, of course, evoke books of all grades. Unless we are willing to let the latrine method of diffusing information be replaced by equally reprehensible pornographic printed material, it behooves us to support such books as this, written in a dignified, accurate, instructive yet interesting style, by one whose professional position is in itself a guarantee. A judicious mixture of the historical approach (chiefly incorrect superstition) and modern science, with frequent reference to lower animals, has allowed the author to achieve his aim of offering in a readable way knowledge of a vital process which human beings should understand. The subject matter is divided into six parts: How Life Begins; Sexual Rhythms; Male and Female Sex Determination; Sterility and Fertility; Twins. In the interesting account of conjoined twins, it should be stated that examination of the original Siamese twins was concluded at the Mütter Museum of the College of Physicians (not of the University of Pennsylvania, as stated). E. K.

A THEORY OF THE FORMATION OF ANIMALS. By W. T. HILLIER, M.R.C.S., L.R.C.P. Pp. 166; 98 text illustrations and 7 full-page plates. Baltimore: William Wood & Co., 1933. Price, $3.00.

THIS develops Laurence Oken's theme that every animal really consists of two animals, a "capital" and a "genital," using, of course, better evidence and arguments than were available in the early 19th century. The fore limbs belong to the head animal, the hind limbs to the other; the salivary gland to the former, the pancreas to the latter and so on. The dual constitution of the fertilized ovum and the two layers of the gastrula are invoked and examples taken from the annelid Polygordius and the common herring. The book attempts thus to explain the formation especially of genera but is not convincing. E. K.

MATERNAL MORTALITY IN NEW YORK CITY. A Study of All Puerperal Deaths, 1930–1932. By the New York Academy of Medicine Committee on Public Health Relations. By RANSON S. HOOKER, M.D., F.A.C.S. Director of the Study. Pp. 290; 89 tables. New York: The Commonwealth Fund, 1933. Price, $2.00.

IN this study, 2041 deaths were reviewed, of which 1343 (65.8%) were held to have been preventable. In the latter group, the physicians were adjudged responsible in 61.1%, patients in 36.7 and midwives in 2.2; indeed, an indictment of and a challenge to the medical profession of New York. Among the factors relating to the physician's responsibility may be mentioned incompetence, lack of judgment and skill, and carelessness. Unsupervised activity of interns is regarded as an appreciable factor. Failure on the part of patients to avail themselves of facilities freely offered, and their lack of coöperation, contributed more than one-third of the deaths.

The subject of preventability is thoroughly discussed, with illustrative case histories under various headings. In a review of the principal causes of death are included the influence of anesthesia, operative delivery, Cesarean section, a comparison of hospital and home delivery, a study of the midwife and an analysis of the patient's economic status.

Specifically, regarding the three great causes of puerperal deaths, it is shown that for septicemia 75 % were judged to be preventable; of these, the physician was held responsible for 81%. In the hemorrhage group, 76% were judged to be preventable; of these, the physician was held responsible for 76%. In the albuminuria and eclampsia group, 72% were judged to be preventable. Of these, the patient was held responsible in 69%. The conclusions and recommendations merit the serious consideration of all who are concerned in the problem of public health and, especially, maternal welfare. There can be little doubt that the final statement would apply to any large city in the United States. "The hazards of childbirth in New York City are greater than they need be. Responsibility for reducing them rests with the medical profession." What does the profession propose to do about it? P. W.

BOOKS RECEIVED.

NEW BOOKS.

Life of Christian Samuel Hahnemann, Founder of Homoeopathy. By ROSA WAUGH HOBHOUSE. With a Preface by SIR JOHN WEIR, K.C.V.O., M.B. Pp. 288; illustrated. London: The C. W. Daniel Company, 1933. Price, 7/6.

Medicine in Virginia in the Nineteenth Century. By WYNDHAM B. BLANTON, M.D. Pp. 466; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1933. Price, $7.50.

Wilhelm Conrad Röntgen and the Early History of the Roentgen Rays. By OTTO GLASSER, Cleveland Clinic Foundation. With a Chapter "Personal Reminiscences of W. C. Röntgen" by MARGRET BOVERI, Berlin. Pp. 494; 96 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $6.00.

Birth Control in Practice. Prepared Under the Supervision of a Scientific Advisory Committee. Text and Tables by MARIE E. KOPP, PH.D., with a Foreword by ADOLF MEYER, M.D. Pp. 290; 50 tables. New York: Robert M. McBride & Co., 1934. Price, $3.75.

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PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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STUDIES ON HEMOLYTIC STREPTOCOCCI.

THE importance of hemolytic streptococci in human and animal infections is reflected in the literature in that, even for 1 year the number of reports on these microörganisms forbids adequate analysis in any relatively limited review. OKELL (*Lancet*, 1932, **1**, 761, 815, 867), in an extensive survey, clearly indicated a number of the outstanding problems and gave his reasons for believing in the essential unity of the human hemolytic streptococci. Methods of fermentation or agglutination had not been found of value in differentiating species within the group. The position of S. "epidemicus" and certain hemolytic streptococci of animal origin had not yet, however, been clearly defined. He considered three properties of the human hemolytic streptococci as characteristic of their pathogenicity under the headings: 1. Production of an erythrogenic (or rash producing) toxin immunologically identical for all strains and which is neutralized by "scarlatinal antitoxin." 2. A pyogenic property perhaps related to streptococcal hemolysin to which there is no effective antibody. 3. An invasive property which may or may not be linked with the pyogenic property and to which antibodies, to particular strains only, are available. These elements in the development of infections vary in intensity from case to case and this variation, together with that in the host's defense, accounts in his opinion for the different pathologic and clinical patterns of human streptococcal disease. The allergic conception of scarlet fever he considered had little to recommend it.

The survey of some of the recent (1933) contributions to our knowledge must perforce be short but will be based chiefly on further developments since Okell's analytical paper. The further attempts to differentiate hemolytic streptococci of human origin into groups which could be correlated in any useful way with types of human disease or localization of the infective process have not been very successful. EDWARDS (*J. Bacteriol.*, 1933, **25**, 527), however, continuing his earlier studies, was able to distinguish hemolytic streptococci of human from

those of animal origin in 96%, using 173 of animal (chiefly equine) and 75 of human origin. He felt nevertheless that a final separation of human and animal strains has not yet been effected. The human strains as a rule fermented trehalose but not sorbitol and gave a pH value in glucose broth of 5.8, while animal strains produced acid in sorbitol and only rarely in trehalose with a pH value in glucose broth of 5 to 5.2. The presence of capsules on the majority (159 Type A) of animal strains and their frequent mucoid colonies make them indistinguishable from *S. epidemicus* and Edwards is of the opinion that these animal strains are not the causative agents of septic sore throat. A small group (8 *S. equi*) failed to ferment either sorbitol or trehalose and also produced no acid from lactose. This failure of *S. equi* to ferment lactose was also emphasized by HAUPT (*Centralbl. f. Bacteriol., Orig.*, **128**, 110, 1933). LANCEFIELD (*J. Exp. Med.*, 1933, **57**, 571) has gone further in a study of 106 strains of hemolytic streptococci from man, other animals, milk and cheese. These included a number of Edwards' strains and other carefully studied cultures from many laboratories. She used precipitin tests with hot hydrochloric acid extracts of the bacteria as antigens and the sera of rabbits immunized with formalinized cultures and was able to classify all but two of the strains into five distinct groups. Group A (23) strains were chiefly human; B (21) high acid producing sodium hippurate-hydrolyzing varieties from bovine and dairy sources; C (49) from a variety of animal sources including those strains of bovine origin which attained a final pH of about 4.8 and did not hydrolyze sodium hippurate; D (8) from cheese only; E (3) from certified milk. She found a striking correlation between her serologic methods and the biochemical and cultural reactions and gave tables showing the results of the reduction of methylene blue milk, growth on 10 and 40% bile agar, fermentation of trehalose and sorbitol and lysis with a streptococcus bacteriophage from sewage, in addition to the tests mentioned above. The specificity of the precipitin reaction was probably, she thought, dependent upon chemically related but serologically specific substances—the group specific substance in the human strains, Group A being of carbohydrate nature as was also that in Group B, and in the other groups this had not been determined. Agglutination would not appear to be as satisfactory for many reasons. MUELLER and KLISE (*J. Infec. Dis.*, 1933, **52**, 139) used it in a classification of 225 hemolytic streptococci of scarlet fever, and found two-thirds of these fell into six well defined groups which were seldom found in normal throats not in relation to streptococcic disease. These authors considered agglutinability as a reasonably constant attribute of hemolytic streptococci.

Not many new technical methods for growing hemolytic streptococci from patients have appeared during the last year. ALIVISATOS (*Centralbl. f. Bakteriol., Orig.*, 1933, **129**, 111), in a study of blood cultures in cases of puerperal sepsis, believed the bactericidal activity of the blood was the greatest cause of failure. He advocated the use of 20 cc. of citrated blood, which he divided into two lots, one of which was added at once to 100 cc. of 1.5% dextrose bouillon (Method A), the other was centrifuged 12 to 15 minutes, all but about 1 cc. of the supernatant fluid was carefully withdrawn and the remainder seeded as above (Method B). The latter method (B) gave positive cultures 36% more often than the former method (A). ROBINSON (*Am. J. Surg.*,

1933, **20**, 131), in a paper on the revaluation of prevailing theories and principles of puerperal infections, pointed out that pathogenic bacteria do not ordinarily multiply in the blood stream of human beings but in the septic focus from which they enter the lymph and blood streams at intervals. The failure to recover bacteria from the blood in outspoken cases of bacteremia he believed due to taking the blood during or just after the chill rather than 3 to 5 hrs. before its occurrence and to the neglect of making anaërobic cultures. The identification of hemolytic streptococci in cultures from maternity cases has been considered, as a rule, relatively easy, but FRY (*J. Pathol. and Bacteriol.*, 1933, **37**, 337) refers to a number of cases from which he was able to isolate typical Beta hemolytic streptococci from the blood or uterus, while from other foci in the same persons strains were recovered which only gave green discoloration on horse blood agar when grown aërobically and which gave no green but a marked Beta hemolysis under anaërobic conditions, and these formed soluble hemolysin in horse serum broth. He also found a number of other interesting variant strains. The possibility that mixed cultures accounted for his results was considered and discarded. The author advocated using anaërobic plates or digging into the blood agar in all primary cultures in order to avoid missing such strains. The importance of anaërobic streptococci is well recognized, but since it is rare for these strict anaërobic strains to produce hemolysis they will not be discussed in any detail in this survey. COLEBROOK and HARE (*J. Obst. and Gynec. Brit. Empire*, 1933 **40**, 609), reported on their association with puerperal fever, in which they considered them next in importance to the aërobic hemolytic streptococci. He found only 2 strains out of some 60 studied which gave hemolysis on the surface of blood agar plates anaërobically.

The problem of dissociation of hemolytic streptococci is especially important, as it concerns the diagnosis of the strains at the time of isolation. It is too complicated a subject to deal with here in any profitable way. SPASSKY (*Centralbl. f. Bakteriol., Orig.*, 1933, **128**, 251) has described and illustrated dissociation forms of laboratory strains of scarlet fever streptococci in which the changes were associated with the development of daughter colonies about the normal smooth colony, or the phenomenon of lysis of the colonies. The direction of change was always from S to R, the reverse never being observed. The R form no longer caused hemolysis with various kinds of blood, was biochemically less active, produced no toxin and the morphology became like that of the diphtheroid bacilli. On the other hand, PILOT and STOCKER (*Proc. Soc. Exp. Biol. and Med.*, 1933, **31**, 181) reported a non-hemolytic variant of a scarlet fever strain originally obtained from the infected udder of a cow, the milk of which had been held responsible for an epidemic of scarlet fever and which retained its property of producing toxin specific for scarlet fever. At first this strain resembled *S. epidemicus* with mucoid colonies and capsules and it, with another similar strain obtained from a sporadic case of scarlet fever, was studied by PILOT and DAVIS (*J. Infec. Dis.*, 1933, **53**, 29) and differentiated to their satisfaction from *S. epidemicus* by toxin neutralization tests. The toxins of these mucoid scarlet fever strains corresponded to the scarlet fever and not to the *S. epidemicus* toxin. They refer to having recently isolated, from cases of erysipelas, hemolytic streptococci which resembled the above mucoid types and suggested that all these may represent

variation or mutation forms and that they may be more virulent than the "normal" form.

The interrelationships between the strains of hemolytic streptococci from scarlet fever, erysipelas and puerperal fever have received perhaps most attention, and the property of producing erythrogenic toxins has been used both to prove and to disprove the unitarian interpretation. WADSWORTH (*Canad. Pub. Health J.*, 1933, **24**, 1), said: "The etiological relationship of the streptococci to puerperal fever, septic sore throat and erysipelas is no longer questioned, but claims identifying a specific streptococcus as the incitant have been practically abandoned. Traditional conceptions of scarlet fever as a specific disease must give way if the streptococcus is to be accepted as the incitant. Scarlet fever and erysipelas are now in practically the same category, that is, must be regarded simply as different manifestations of streptococcus infection developing under special conditions of tissue susceptibility, since there is no known method of distinguishing between the so-called *S. scarlatina* and the *S. erysipelatus*." After studying the toxins of at least 1000 strains of hemolytic streptococci and attempting to group them according to the reactions of the tissues of different animal species to the toxins and also by the extent to which they are neutralized by immune sera or antitoxins, he concluded that no one group was associated specifically with any particular symptom complex but quite the contrary, so that representatives of the several groups were found in the different diseases incited by the streptococci.

All this suggested to him "that subtle conditions of tissue susceptibility underlie the mechanisms of these reactions." Virulence is not necessarily related to toxin production and there are many other unsolved problems for the future. The important practical point is that therapeutic serum should be potent and of wide valency. The demonstration of TRASK and BLAKE (*J. Am. Med. Assn.*, 1933, **101**, 753) of a toxin from 3 severe cases of scarlet fever in which potent scarlatinal antitoxin was ineffectual, confirmed the earlier views on the heterogenicity of toxins and antitoxins in man, and it is significant that Wadsworth has prepared a polyvalent antitoxin which includes this new toxin, the standard Dick toxin, and many others in its range of neutralization.

There are many difficulties in the interpretation of the skin tests, difficulties associated with titration, neutralization by antitoxin and individual differences in the reactions of human and animal subjects. KRESTOWNIKOWA and RJACHINA (*Ztschr. f. Immunitätsforsch. u. exp. Therap.*, 1933, **78**, 414) compared the purified toxins prepared from the Dochez strain of the scarlet fever streptococcus (having found this strain a stronger toxin producer than the Dick 8 strain) and from the Birkhaug strain of the erysipelas streptococcus. The preparations were freed from protein, and then purified by a series of dialyses, alcoholic precipitations and dryings to a constant weight with yellowish, rather hygroscopic powders as the products. These materials were susceptible to oxidation, contained a reducing substance set free acid hydrolysis, had part of the nitrogen in the form of aminon gen, showed a free carboxyl group and were levorotatory. The scarlet fever and erysipelas toxins thus purified showed chemical differences, the amino-nitrogen being lower, the angle of rotation being less, and the reducing substance being more easily destroyed in the erysipelas than in the scarlet fever preparations, but as the purification was made more

perfect the two substances became more alike. The two purified toxins in immunity reactions with specific sera (precipitin reactions with convalescent and animal antisera being particularly clear cut) complement binding and neutralization tests showed the two substances to be very similar if not identical. The toxic characteristics were always more marked with the scarlet fever than with the erysipelas substance, the latter, however, always produced severe cramps in rabbits which the former did not do. They considered the problem of identification as still unsettled.

The differences between the toxicogenic powers of different strains of streptococci from scarlet fever, erysipelas or other infections make one hesitate to lay too much stress on relatively slight qualitative differences until the essential criteria have been more clearly enunciated. The complete story of the infections by the hemolytic streptococci cannot be completed without supplementing our knowledge concerning the erythrogenic toxin with that of other offensive weapons of the streptococci and a more careful clinical study of the patients, subject to such infections, regarding the nature of their response to the streptococcus antigens. Day (*J. Pathol. and Bacteriol.*, 1933, **37**, 169) reported his experience with an antigen which was obtained from virulent cultures of streptococci both hemolytic and non-hemolytic and which he called V antigen. This antigen, quantitatively related to virulence, was type specific and was obtained by the use of $\frac{N}{20}$ hydrochloric acid at 60° C. There was evidence that it protects the bacteria from phagocytosis. It was formed during active growth, was attached to the cocci, was resistant to acid, was destroyed by alkali and heat and bacterial enzymes and was readily adsorbed to protein. It was antigenic and excited active immunity while the sera of immunized animals gave a passive immunity. It was suggested that the substance is of the nature of a protective secretion attached to the cocci.

Considerable advance has been made in our knowledge of hemolysin. Todd (*J. Pathol. and Bacteriol.*, 1933, **36**, 435) found the addition of serum to broth permitted the production of a streptolysin by the cocci which had characteristics distinctive from that produced in broth without serum. The two are equally hemolytic and both are antigenic. The hemolysin formed in serum-free broth is so sensitive to oxidation that reducing agents must be used to demonstrate its total content, it is easily adsorbed by filters and readily combines with its specific antibody. The lysin produced in serum broth is more stable, relatively resistant to oxidation and reduction, resists adsorption and combines very little with its antibody. He believed the reason hemolysis does not occur *in vivo* is because the serum-hemolysin is neutralized by lecithin (Gordon and Stansfield, 1929). Todd, Laurent and Hill (*J. Pathol. and Bacteriol.*, 1933, **36**, 201) studied the relationship between streptococcal antitoxin and antistreptolysin, and showed they were distinct and separate antibodies. Swift and Hodge (*Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 1022), by adding filtered salts, buffers and glucose to beef-heart peptone broth previously sterilized at 100° C., obtained a medium which gave extremely heavy bacterial growths and a good yield of streptolysin. Hodge and Swift (*J. Exp. Med.*, 1933, **58**, 277), considerably improved the method for titrating antistreptolysin by showing that streptolysin might have varying hemolytic but constant combining capacity. It being the reduced streptolysin which

exhibits hemolytic activity, they used sodium hydrosulfite as a reducing agent and noted that the yield of hemolytic streptolysin continued to increase for 24 hrs. *in vacuo*, but that it was impossible to reduce all the hemolysin so as to give a constant hemolytic titer corresponding to the combining power, suggesting that a part of the hemolysin may have been altered to an irreversible form. However, it could be reduced, remained stable for months if stored in the ice-box under vaseline and could be used as a standard in titrating antistreptolysins.

The varying sensitivity of the tissues to streptococci both hemolytic and non-hemolytic and to their products has received considerable attention. Böhmig and Swift (*Arch. Path.*, 1933, **15**, 611) noted that rabbits, after prolonged intravenous inoculation with streptococci became hypoergic or immune, but if inoculated intracutaneously they became hypersensitive. They showed that there was a definite relationship between hemolytic streptococci and *S. viridans* in these tissue responses in the skin to a later intracutaneous inoculation. Rabbits made hypersensitive to green streptococci were one hundred times more responsive, as determined by size of the lesion, to homologous streptococci and showed more marked edema, tissue destruction, abscesses, capillary endothelial swelling and more marked monocytic infiltration than did normal or immunized animals. The response to whole microorganisms, they emphasized, was different from that to one or more of its components. McGibbon (*Lancet*, 1933, **2**, 1363) used an extract free from soluble toxin—a "nucleoprotein endotoxin"—and tested the cutaneous reactions in cases of scarlet fever and erysipelas. Because of the development of these reactions during convalescence they were considered of allergic nature. In cases in which the Dick test tended to remain positive, allergy was slow in appearing. The reaction in erysipelas was not so well marked as in scarlet fever, but it was more like erysipelas itself; there was, however, no actual pain, nor did blebs develop. Seegal, Heidelberger, Jost and Lyttle (*Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 582) used the precipitin test with 172 sera of well persons and 138 from those with various diseases—*S. viridans* endocarditis, rheumatoid arthritis, hemolytic streptococcus diseases, acute, subacute and healed glomerular nephritis and cases of peptic ulcer. Two protein fractions and the group carbohydrate of *S. hemolyticus* and the nucleoprotein of *S. viridans* served as antigens. There was little or no precipitin in the normal group to any of the fractions. In the cases of subacute *S. viridans* endocarditis or rheumatoid arthritis there was strong precipitin formation against the hemolytic streptococcus protein antigens, which was moderate in the hemolytic streptococcus diseases, acute and subacute glomerular nephritis, and peptic ulcer. The reactions to hemolytic streptococcus carbohydrate was strongest in the hemolytic streptococcus infections or rheumatoid arthritis. The endocarditis cases alone gave marked precipitin formation against *S. viridans* protein. There are many valuable facts in this report, but their correct interpretation must await fuller knowledge of the factors concerned.

Hooker (*J. Immunol.*, 1933, **24**, 65) did not consider the arguments in favor of the allergic interpretation of scarlet fever, nor the objections to the toxin-antitoxin hypothesis, to be well founded. He looked upon cutaneous allergy as a local expression of an enhanced capacity for an unusually rapid development of specific resistance. He further cited

the evidence which shows that allergic inflammation delays bacterial invasion and hastens healing.

The unsettled differences of opinion regarding the relationship of hemolytic streptococci to acute rheumatism and rheumatoid arthritis must be left for another review.

The discovery of the fibrinolytic action of hemolytic streptococci by TILLET and GARNER (*J. Exp. Med.*, 1933, **58**, 485) seems full of promise as a help in making clearer the interpretation of many streptococcus diseases. The fibrinolytic capacity of hemolytic streptococci would appear to be an important offensive weapon of these microörganisms in their attack on the body. The active principle was filtrable and acted apparently only on normal human fibrin clot, which may serve as still another method of differentiating human from animal strains. It was extremely active requiring, as a rule, about 2 to 10 min. completely to dissolve the clot. *S. viridans* strains were inactive, as were some 30 other bacterial species. The plasma of patients recovered from acute hemolytic streptococcus infections they found to be highly resistant to fibrinolysis, and also that it can convey to normal plasma clot the same antifibrinolytic property. Rabbit fibrin clot was insusceptible to its action, but if human thrombin were used to produce the clot, fibrinolysis was no longer inhibited, which fact offers a means further to analyze the phenomenon. The presence of fibrin in the reaction zone at the primary focus of infection is usually considered as helping to prevent the entrance of streptococci into and along the lymphatics, so that, if this barrier is removed by the fibrinolytic agent, this may be another of the long sought factors which determine the invasive capacity of hemolytic streptococci.

The year's progress in the study of this important group of bacteria as indicated in this brief and incomplete review has been, we believe, very substantial and has opened many hopeful roads for future investigations.

HYGIENE AND PUBLIC HEALTH

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AMEBIC DYSENTERY.

AMEBIC dysentery generally has been regarded as a disease of warm climates, although it has been recognized as occasionally occurring elsewhere; indeed, a rather large number of cases has been reported from temperate climates. The recent outbreak, which had its origin in Chicago, shows that it is necessary to revise this and other conceptions of the disease generally held. New light also has been thrown on its mode of transmission. Hitherto the means of infection have

been rather obscure. Contaminated water and food have been incriminated as vectors, but without very conclusive positive evidence. Vegetables from southern sources have been accused. Convalescents or healthy carriers shedding ameba cysts have been suspected, but no very definite evidence has been brought forth to show that this mode of infection is important. The recent outbreak, which began in Chicago during the summer of 1933 and continued on into the autumn, had several features interesting from different points of view, notably from the epidemiologic and clinical aspects. The coincidence of the Century of Progress Exhibit and the paucity of early information on the subject added to the gravity of the situation. Approximately 800 cases throughout the country have been identified as having had their origin in Chicago, and the large majority of these has been traced to a single hotel. An intensive laboratory study of the food handlers in this hotel showed an extraordinarily high incidence of ameba carriers; and combined laboratory and clinical examinations demonstrated a number of active cases of the disease, though usually not with very pronounced symptoms. A study of the water supply and of the sewage disposal system of the hotel incriminated demonstrated the probability of sewage contamination of drinking water.

Clinically, the cases were not all of the typical textbook patterns, but they fell within the well-recognized deviations. These variations extended all of the way from mild abdominal discomfort with either diarrhea or constipation to rather severe manifestations with tenesmus, bloody and mucous stools, toxic symptoms and death. Many of the cases were mildly febrile and in a few the temperature was rather high for amebic dysentery.

Perhaps the most interesting clinical feature was the fact that a good many of the cases were mistaken for surgical conditions and even subjected to surgical intervention. The most common erroneous diagnosis from a surgical point of view was appendicitis; some cases were suspected of being cholecystitis; and a smaller number were regarded as possibly malignant in nature. Perhaps the commonest error was to regard cases as non-specific "colitis" or "ulcerative colitis." The mortality was high in the cases subjected to operative procedures. The high incidence of erroneous diagnoses demonstrated in this outbreak prompts one to suspect that isolated cases not associated with a general outbreak may also often pass under incorrect diagnoses.

The incubation period, which could be fairly accurately established in many cases, usually has varied from a week to 3 months, with the majority of patients falling ill within 3 or 4 weeks after exposure.

The onset may be rather sudden and stormy, or may be manifested only by vague abdominal distress. Stools may vary from those normal or practically so to those made up largely of mucus and blood; or there may be only an increase in the number of stools. The Roentgen ray findings may be suggestive of other conditions. Under appropriate treatment the symptoms usually clear up rapidly, but if the condition is not recognized promptly it may become chronic or recurrent.

The case mortality in the present outbreak has been around 5%.

The laboratory aspects of the cases are interesting. A blood count does not give much assistance in eliminating surgical conditions, since a leukocytosis is not rare. The detection of amebas in the stool is of aid in diagnosis. In acute cases the motile protozoa containing red

blood cells offer little possibility of confusion with other organisms. The cystic stage, however, which is the common phase in the life cycle found in the carrier, is not so readily differentiated from non-pathogenic amebas—indeed, it is perhaps not an exaggeration to say that only an expert protozoölogist, or a technician who has been thoroughly trained by an expert, should attempt this differentiation. In some cases, material secured by proctoscopic examination may show organisms that would have been missed otherwise.

Repeated stool examinations may be necessary in clinical cases and in carriers without manifest symptoms. A single negative examination is to be given but little weight, and even repeated examinations may give misleading negative results. Perhaps one would be warranted in saying that, in the presence of tenesmus associated with blood and mucus in the stools, clinical manifestations should be given greater weight than negative laboratory findings. On the other hand, the presence of amebas, particularly the encysted form, does not necessarily prove that the clinical condition present is due to amebas. Serologic methods of diagnosis have not been sufficiently worked out to be applied clinically, and the same may be said of the cultivation of the amebas. It is well known that a considerable percentage of the general population of this country (some authorities say from 5 to 10%) harbors amebas, and it will readily be perceived that in any considerable group of cases of any disease some ameba carriers will be found whose clinical conditions might in no wise be related to the presence of the parasites.

There have been material advances in the treatment of this disease within comparatively recent years. For the relief of symptoms of acute manifestations, including hepatitis, the use of emetin in doses of 1 mg. per kilo daily, over a period not exceeding 10 days, appears to give the best results. Care must be taken in the use of the drug since it is highly toxic, and an interval of at least 10 days should elapse between series of injections.

In the treatment of the carrier condition, most satisfactory results have been obtained with some of the later drugs, such as chiniofon (0.25 to 1 gm., by mouth, thrice daily) or carbarsone (0.25 gm., twice daily).

In the present outbreak, cases have been predominantly in adults, and largely among those of the more comfortably situated group from the economic point of view.

It has been recognized that amebas are likely to become widely distributed in families once the infection is implanted in a member of the family group. It is too early to say whether secondary foci are likely to develop as a sequel to the Chicago outbreak. We are still in ignorance of many factors governing transmission.

Two explanations have been advanced to account for the sharp outbreak forming the basis of this discussion: (*a*) That a strain of Endamœba histolytica of unusual virulence was imported or developed among food handlers in Chicago, or (*b*) that a bacterial organism living in symbiotic relation with the amebas accounted for the high virulence of the strain and possibly for some of the symptoms. Whether either of these considerations is important cannot be stated at present.

From the purely public health point of view, theoretically, prophylaxis should be very simple. The necessity for remedying conditions lead-

ing to possible contamination of a water supply is obvious. The examination of food handlers occurs at once as the logical procedure when epidemiological evidence points to this source of infection, but practically this is not so easy. The number of examinations required before an individual is to be considered negative multiplies the work very materially. In practice, so large a number of food handlers are found infected that their hospitalization and treatment assume proportions too large to be dealt with ordinarily in a satisfactory manner. In addition, there are few technicians sufficiently well qualified to render dependable opinions on intestinal protozoa. It has been estimated that a skillful, capable and experienced technician can examine only 8 to 10 specimens a day, and as the number of food handlers in any city may run as high as 5% of the population, the time required and the work involved obviously make it a difficult, or impossible, procedure. The problem is further complicated by the well-known fact that carriers may be found free of recognizable amebas in stool specimens for long periods, only to have them reappear at later examinations. A food handler who was known to be an ameba carrier in 1927 was found to be involved in the most recent outbreak, though there had been a number of negative stool examinations in the interval. It is the carrier rather than the clinical case who spreads the infection. On the whole, therefore, the examination of food handlers appears to be impracticable.

It is interesting to note that in the present outbreak, flies have not been mentioned as an agency of transmission. This suggests that they may be much less important than had been thought by many.

A mode of attack on the problem of transmission is through improvement in sanitary conditions surrounding food handlers, such as installing adequate toilet and washroom facilities and taking measures to require personal cleanliness on the part of food handlers. These means do not seem to have been altogether successful in Chicago, probably because contamination of the water supply, which was not recognized early, seems to have been the most important factor in the outbreak. There are stumbling blocks which are not to be ignored. Perhaps the chief obstacle lies in the difficulty in creating a sustained effective interest on the part of any group in careful systematic cleansing of the hands after a visit to the toilet. Probably few persons could be sufficiently convinced that they are a source of danger to others to impel them to take the measures (such as hand scrubbing or the wearing of gloves) that would be necessary to protect others.

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PHYSIOLOGY

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The Changes in Total Content and Osmolal Concentration of Glucose and Chlorid After the Ingestion of Glucose by Diabetic Patients.—F. WILLIAM SUNDERMAN and E. S. WILLIAMS (Laboratory of Research Medicine, University of Pennsylvania). After the ingestion of glucose by diabetic patients the concentration of glucose in serum was increased and the concentrations of total fixed base and of chlorid were decreased. When calculations were made which permitted an estimation of the change in the total content of these components in the serum, it was found that the amounts of glucose, chlorid, and water of the serum were all increased after the administration of glucose.

The experiments suggest that glucose entering the serum following glucose ingestion tends to draw water from the tissues. The water added to the serum with the glucose and from the tissues dilutes the serum electrolytes and sets up a potential gradient for electrolyte from tissue to serum, resulting in an inflow of chlorid. As the glucose is built up into glycogen or otherwise removed the potential gradient will tend in time to be reversed and electrolyte will pass from serum to tissues. The experiments illustrate the fact that a potential gradient induced with respect to a single component induces a gradient with respect to all the other components and sets them moving in one or the other direction.

The Spectral Sensitivity of Single Visual Sense Cells.—H. K. HARTLINE (Eldridge R. Johnson Foundation, University of Pennsylvania). The effect of various wave-lengths of visible light in the stimulation of single visual sense cells has been studied by Dr. C. H. Graham and myself, employing the single-fiber preparation from the eye and optic nerve of *Limulus*. Oscillographic records were made of the discharge of impulses in a single optic nerve fiber, in response to stimulation of the attached sense cell by light from different regions of the visible spectrum. Wratten Monochromatic Filters supplied the spectral lights, the total intensity transmitted by each filter being determined by means of a thermopile.

The response of the single visual sense cell does not vary qualitatively with wave-length of stimulating light; by properly adjusting the intensity, responses can be obtained which are identical, impulse for impulse, for all the spectral lights used. The reciprocals of these intensities necessary to produce a constant response, plotted against wave-length, give the visibility curve of the single sense cell. This curve is symmetrical about a maximum at approximately 520 μ, falling off to low values in the red and in the violet. It closely resembles the visibility curve of human rod vision, with the maximum somewhat displaced.

Bundles from the optic nerve, containing several active fibers whose impulses can be distinguished by differences in size and shape, were used to determine whether there is any differential sensitivity among

the sense cells of the same eye, in different regions of the spectrum. Such a differential sensitivity has been found to exist in the eye of *Limulus*, and may be considered a peripheral mechanism of color vision.

Studies on the Heart and Circulation in Disease; Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in 235 Subjects.—Isaac Starr, Jr., J. S. Donal, A. Margolies, R. Shaw, L. H. Collins and C. J. Gamble (Laboratory of Pharmacology, and the Medical Division of the University Hospital, University of Pennsylvania). This study was made possible by the development of the katharometer method for the analysis of ethyl iodid by Donal and Gamble. This improvement so greatly increased the rapidity with which cardiac output could be estimated that over 500 determinations have been made on 235 subjects. These included 31 healthy persons and 204 patients from the wards of the University Hospital. The data contain groups of patients with intercurrent disease not affecting the circulation, with anemia, hypertension, hyperthyroidism, and neurocirculatory asthenia, also a few cases of Addison's disease, myxedema, and arteriovenous communications. Cases of various types of heart disease were studied also, *e. g.*, patients who had once been decompensated, cases of valvular disease, of arrhythmia, of coronary occlusion, of angina pectoris, and of aneurysm. On the other hand patients with acute cardiac decompensation, with advanced pulmonary disease, or with fever, were not studied.

The results have been subjected to statistical analysis. By this means the relationship of the cardiac output to age, sex, body surface, body weight, and heart size has been studied. The normal limits of cardiac output, heart work, stroke volume and arteriovenous oxygen difference have been defined, and the deviations in disease noted. These values give information concerning the circulation, but throw little light on the condition of the heart.

The most promising method of detecting myocardial disease is by the relationship of heart work per beat to heart size, an extension of Starling's "Law of the Heart," to clinical conditions. The normal limits of this relationship have been defined: healthy persons, patients with disease not affecting the circulation, and patients with disease of the circulation but with presumably normal hearts, give values within the normal range. But in patients with undoubted myocardial disease (who had once been decompensated) this relationship is abnormal almost without exception.

The Action of the Pyloric Sphincter.—Harry Shay and J. Gershon-Cohen (Gastro-intestinal Clinic of Jewish Hospital and Laboratory of Roentgenology, Graduate Hospital, Philadelphia). Our experiments have consisted of a roentgenologic study of gastric emptying and pyloric behavior in man following the gastric and duodenal application of various test substances. While many reagents were studied, this report is primarily concerned with the action of acid and alkali in 176 serial Roentgen examinations in 24 patients which indicate that:

1. Without due consideration to the individual gastric secretory response no proper evaluation of the experimental results could be made.

2. Of the three components concerned in gastric emptying, gastric peristalsis plays an incidental rôle only and is not concerned with pyloric

opening; gastric tonus is the greater motivating force, but the potency of each depends entirely upon the state of the pylorus.

3. When the stomach is empty, the normal state of the pylorus is that of relaxation. This is always seen in achlorhydrics, but does not obtain in patients with free gastric acid.

4. The hydrochloric acid of the gastric contents is the natural intrinsic agent responsible for pyloric action. We do not imply, however, that it is the sole possible agent. Certain other ingested substances, such as various irritants, fats, hyper- or hypotonic solutions of sugars and neutral salts, through their chemical or physical action are equally efficacious.

5. Any agent (intrinsic or extrinsic) becomes effective in producing pyloric closure only upon reaching the duodenum. Here a reflex is activated and maintained until proper neutralization or dilution of the duodenal contents which makes it acceptable to the adjacent distal duodenum, has occurred. Then pyloric relaxation takes place.

6. The duodenal mucosa adjacent to the cap is most responsive to stimulation, though the response may be obtained in other portions as well. In general, the farther from the cap, the stronger the stimulus necessary to evoke the pyloric response.

7. Under normal conditions, the duodeno-pyloric reflex is not dependent upon duodenal filling.

8. Evidence is presented suggesting that the duodenal neutralizing mechanism is most highly developed in hyperchlorhydrics and least in achlorhydrics.

9. The antrum, pylorus, and duodenal cap appear physiologically to be intimately related.

Were we to picture our concept of pyloric action in a homely simile, as others have been wont to do, we would say that the stomach is like a dumbwaiter ever ready to deliver through its door, the pylorus, anything reaching it. The duodenum, however, sensitive connoisseur, is selective. If the gastric contents are acceptable to the official taster, the duodenal cap, gastric emptying continues uninterruptedly; if not, the door, the "pylorus," is hurriedly closed and stays so until the portion tasted, "Trial portion," is rendered acceptable.

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